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In Pancreatic Islets, Metabolic Stress Affects Pericyte Response to Optogenetic Stimulation.

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Abstract

Glucose homeostasis in the body is maintained by highly vascularized microorganisms in the pancreas. Insulin secretion from beta cells is dependent on the presence of healthy islet vascular cells. Islet pericytes, in particular, have been shown in recent research to modulate local blood flow velocity and to be necessary for beta cell development and function maintenance. Obesity-related changes in islet pericyte shape include an increase in metabolic demand. In this study, we investigated the impact of metabolic stress on the functional response of islet pericytes to stimulation in a mouse model of type 2 diabetes, directly in the pancreas in vivo. We discovered that a high-fat diet produced islet pericyte enlargement without affecting local blood flow in the islets. Pericyte activity was shown to be hindered, despite enhanced expression of genes encoding proteins that are directly or indirectly involved in cell contraction, by optogenetic activation. Beta cell failure in type 2 diabetes may be exacerbated by metabolic stress, according to these studies.

INTRODUCTION

An important part of pancreatic islet function is the functioning of the islet vasculature (1). In addition to ensuring appropriate supply of oxygen and nutrients, the dense capillary network and high blood perfusion (2) provide quick detection of circulating signals that govern hormone release, and rapid absorption of produced hormone into the circulation. Beta cells and vascular cells have an advantaged relationship because of the islet cellular architecture (3). Type 2 diabetes (T2D) etiology has also been linked to disruption of the islet vasculature, it should be noted (1) Different cell types make up the islet capillaries (1). The mural cells that line capillaries, known as pericytes, may have a role in beta cell survival and function as well. Endothelial cells have been widely investigated in this regard (1, 4, 5). Many tissues'

blood flow and vascular stability are influenced by pericytes (6, 7). Platelet-derived growth factor (PDGF) signaling, the release of substances that improve glucose responses, and enhanced insulin granule exocytosis are all supported by pericytes in the islets (12). As an added benefit, beta cell activity depends on islet basement membrane components, which are abundant in islet pericytes (13, 14). Finally, although different vasoactive factors, nutrients and hormones (15), including insulin (5) have long been known to regulate islet blood flow, such regulation was thought to occur mainly at the pre-capillary level (3) and a direct role for pericytes in the regulation of islet blood flow was recently demonstrated (16, 17), providing another level of control in addition to those of feeding arterioles Because beta cells, endothelial cells and sympathetic nerves release glucose and vasoactive chemicals that alter cytosolic calcium concentrations, islet pericytes may regulate capillary diameter (16). Islet function depends on blood flow direction and velocity (18, 19), hence it was postulated that pericytes may help maintain glucose homeostasis by actively regulating islet blood flow. Recent research on diabetic mice treated with streptozotocin and implanted with islets in the anterior chamber of the eye demonstrated that the pericytes regulation of blood flow in islets alone is sufficient to regulate appropriate hormone output and systemic blood glucose levels (17). Islet blood flow is disrupted in situations of poor glucose tolerance and type 2 diabetes (T2D) (19, 22–24), according to compelling evidence (14, 20, 21). Diabetes retinopathy and peripheral neuropathy have an early morphological signature in the loss of pericytes, which is an important part of peripheral diabetic vascular problems (25). (26, 27). In mice and rats with insulin resistance and T2D (23, 28), the pericytes in the islets become dilated and hypertrophied, and as T2D advances in mice (20) and humans, the pericyte coverage diminishes (16). However, it is still uncertain whether metabolic stress may alter islet perfusion and function by targeting pericytes. Our findings show for the first time that islet pericyte responsiveness to stimuli is affected by metabolic stress in high fat diet (HFD)fed mice.

SUITABLE MATERIALS AND TECHNIQUES

The European criteria for animal care (2010/63/EU) were followed while doing the research on animals. The Institutional Animal Care and Use Committee (CEEA-LR-1191) and the French Ministry of Agriculture (APAFIS#3875) have both given their permission to the protocols in question. During the research, mice were raised in a standard facility devoid of a

particular infection. Janvier SAS sold the C57BL/6J mice (Le-Genest-St-Isle, France). As well as ROSA26-ChR2(H134R)-td, NG2-DsRed, and NG2-Cre. The Jackson Laboratory provided 29 tomato-colored C57BL/6J mice (Maine, USA). The NG2DsRed animals, which show uniform labelling of both cytoplasmic and cell protrusions in NG2- positive cells, an indicator typically used to detect pericytes, were utilized to examine alterations in pericyte morphology after HFD eating (30). Lightsensitive ion channels were expressed in NG2expressing cells by crossing ROSA26-ChR2tdTomato and NG2-Cre mice. NG2-positive cells in these animals are only labeled with TdTomato at the plasma membrane, which prevents pericyte morphology analyses. Normal (ND) and high fat (HFD) diets were given to 6-week-old mice for 16 weeks, and the results were studied. Only male mice were employed in this study due to the preventive effects of estrogens against high fat diet-induced obesity (31). Experiments included intra-peritoneal glucose tolerance (IPGTT) and insulin tolerance tests (ITT). GSIS tests were also included (32, 33). Before the experiments, mice were fasted for an entire night.

Pericyte Activity Modulation in Vivo

The pancreas was surgically exposed as reported (33–35) in order to study blood flow patterns in vivo. Anesthetized animals were administered ketamine/xylazine (0.1/0.02 mg/g), put on a heating pad, and heart rate was monitored constantly while breathing was regulated via tracheotomy. Metal stage coated with soft polymer, Bluesil, and stainless steel pins (tip = 0.0125 mm) were used to attach the pancreas to the stage. A NaCl 0.9 percent solution heated to 37°C was constantly pumped into the tissue. Intravenous injection of fluorescent dextran molecules (labeled with D2, 70 kDa, 25 mg/ml in NaCl 0.9 percent, 100 l/20 g body weight) was used to mark the vessels. A xenon arc lamp was used to excite fluorescence (300W, Sutter Instruments). An epi fluorescence microscope equipped with a rapid sCmos camera (ORCA Flash4.0, Hamamatsu) and a long working distance objective (2 cm, Mitutuyo, M Plan Apo 20, NA 0.4) was used to capture the fluorescence (36). Computer-controlled light flashes (473 nm) were used to modulate the electrical activity of ROSA26-ChR2-Tomato mice crossed to NG2-Cre mice (37). When compared to baseline settings, the laser pulse length and strength were optimized to reduce blood flow by 50 percent or more (150 ms, 1 Hz, 1400 mA). Optical fiber with a diameter of 200 nm was used to transmit light (473 nm Blue Solid State Laser CNI Laser, Acaltechnology) at a distance of 0.5 mm and with an output power of 10 mW to the tissue. Littermate wild-type (wt), NG2-Cre, and ROSA26-ChR2Tomato mice were used as the controls since the findings obtained from each of these three genotypes were the same.

Data Mining from Images

a single Z axis One-minute videos have been gathered. The frame rate was set at 150 frames per second. 3.8 s before the laser was turned on, we monitored blood flow in resting circumstances. Recording continued for 7 seconds after the final laser flash, which was 150 ms in duration and occurred at a rate of 1 Hz. ImageJ was used to crop the videos before stabilization. For the first time, image analysis tools reported in the literature were used to visualize the movement of RBC shadows (38). Measurements of RBC velocities were made before laser stimulation, at intervals of 1, 2, and 3 s after a laser pulse; and at intervals of 1, 2 or 3 s following the final pulse. The RBC velocity calculation required a minimum of 150 frames. At least three distinct mice per condition had their RBC velocities recorded in five to ten separate vessels throughout each video. ImageJ was used to evaluate changes in vessel diameter generated by pericyte optogenetic activation (line scan function). At least three independent videos from three separate mice per condition were used to quantify five to ten vessels before and after six flashes of laser stimulation.

Isolation of Islet Cells and Real-Time RT-PCR

After collagenase breakdown of the whole pancreas, the pancreatic islets were selected by hand (39). The RNeasy microkit (Qiagen) was used to extract total RNA from mouse islets as per the manufacturer's instructions. With random hexamer oligonucleotides and SuperScriptIII reverse transcriptase, reverse transcription was performed (2,000U; Invitrogen, LifeTechnologies, EUA). Real-time quantitative PCR was performed using Roche's LightCycler® 480 SYBR Green I Master (Roche) in the 7500 System, and the reverse transcription product was diluted according to the efficiency curve (Applied Biosystems). GeNorm was used to choose genes for housekeeping (40). The following criteria were met over the course of the PCR tests: One minute at 65 degrees Celsius and 45 cycles of 95 degrees Celsius for 10 seconds and 72 degrees Celsius for 30 seconds were followed by the Melting Curve. Each gene's ct values were recorded and standardized to the geometric mean

of Ppia, Aldo3, Mrlp32, and Tbp, using the primers provided in Table S1. Based on the ddCT technique, Ct values are presented as a percentage of normal diet-fed animals (ND) (40)

Confocal Laser Microscopy

As mentioned, pancreas was prepared and antibodies were labeled (33). A Zeiss LSM 780 confocal microscope was used to capture the images. To analyze the images, we used Imaris (Bitplane), Volocity (Perkin Elmer), and ImageJ (NIH) (NIH). Each group or animal had four slices randomly chosen, and all of the islets within those slices were studied for quantitative purposes. To begin, this has the potential to detect at least a difference of 1.2-fold with an SD of 40%, power of 0.9, alpha = 0.05 (G*Power 3.1). Clinical Sciences' rabbit anti-Ki67 antibody was used at a 1:100 dilution; guinea-pig anti-insulin was used at a 1:100 dilution from Abcam; mouse anti-glucagon was used from Sigma; rat anti-endomucin was used from Santa Cruz Biotechnology; and alexa 647-conjugated antiaSMA was used from R&D Systems; (1:200,
Abcam). Dapi was used to label the nuclei (Sigma). ImageJ was used to assess the surface area filled by a DsRed pericyte cell body with a nucleus in order to determine the islet pericyte core area. These pictures were split into islet and exocrine tissue surfaces by the number of pericyte cells having a nucleus. It was determined by dividing the number of Ki67+ nuclei in insulin-positive islets by the total number of insulin-positive islet nuclei (33).

Analytical Methods

Mean SEM is used to represent the data. GraphPad Prism was used to conduct statistical analyses. The D'Agostino-Pearson test was used to check for normality, and comparisons were done using either unpaired Student's t-tests or two-tailed MannWhitney U-tests, as applicable. ANOVA and the Bonferroni post-hoc test were used to make multiple comparisons. P-values were regarded to be statistically significant.

RESULTS HFD Alters Islet Pericyte Morphology and Density

To begin, we looked at changes in islet pericyte shape after HFD diet. Because of the broad coverage of NG2DsRed cells in islet capillaries, we chose NG2DsRed-expressing animals (16, 30, 37). (16,
17). Platelet-derived growth factor receptor beta (PDGFRb) was found in the majority of NG2DsRed cells (Figure S1A) (16), and a small percentage of these cells also had contractile smooth muscle actin protein (aSMA) (Figure S1A), which is similar to previous studies showing the heterogeneity of the pericyte population in islets (16, 17). Figure S1B–H shows changes in islet gene expression such as Ins1, Ins2, and Gck (Figure S1B–H) in male mice fed HFD for 16 weeks, which are consistent with previous studies (32, 41–43). Male mice fed HFD for 16 weeks showed obesity, hyperglycemia, glucose intolerance, insulin resistance (Figure S1B– H). the number of pericytes per unit of islet surface decreased and there was an increase in the size of pericytes (Figures 1B, C) as a result of HFD on pericyte morphology in the islets (Figure 1D)The Basal Islet Is Not Required for Capillary Dilation. During HFD, there are changes in the flow of blood via capillaries.According to earlier findings (42), HFD increased islet size and beta cell proliferation (Figures S2A–C) in our transgenic mouse model, which was followed by an increase in islet capillary width (35 percent). Vascular growth factor A (Vegfa), an angiogenic factor that is abundantly expressed in islets (23) and that regulates islet capillary density (44) was unchanged after HFD treatment (Figure S2E), suggesting that vessel dilation rather than angiogenesis occurred, which agrees with the ob/ob mouse model (23). Standard chow- and islet-fed mice had comparable distributions of RBC velocities in individual vessels and islets.

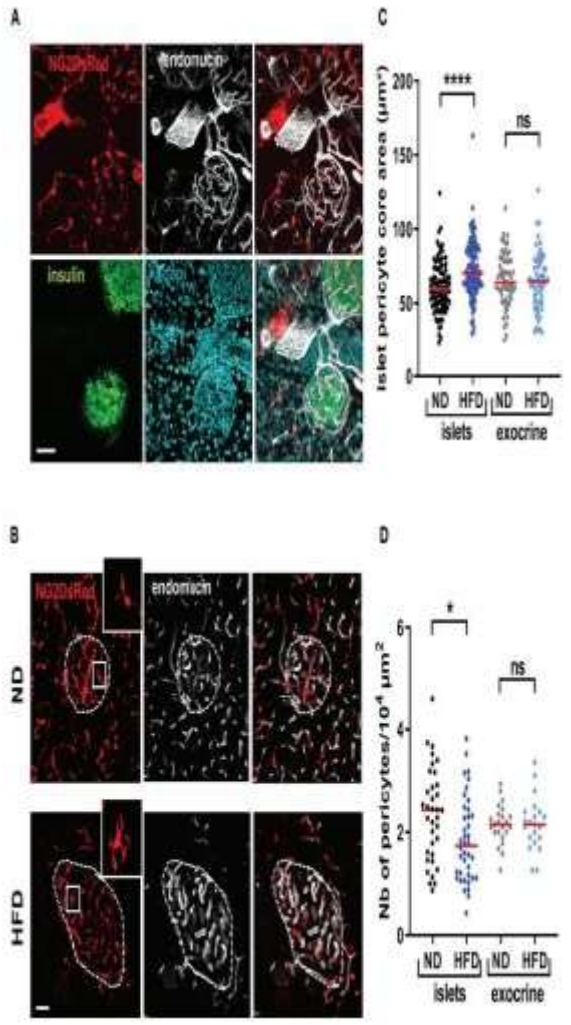

FIGURE:1

Islet pericytes undergo morphological changes after a 16-week HFD therapy. Images of NG2DsRedpositive pancreatic islets from NG2DsRed mice (scale 50m, 30m Z-projection; red: NG2DsRed, green: insulin, white: endomucin, blue: dapi) indicate that the cell bodies and processes of NG2DsRed-positive islets border the capillaries. Pericyte hypertrophy in NG2DsRed animals treated with HFD is shown in (B) a representative confocal picture (scale: 50 m, 20 m Z-projection; red: NG2DsRed, white: endomucin). Enlargements of the boxed sections on the left panels are shown in the inlet images. ND stands for a normal diet, whereas HFD stands for a high-fat one. An ANOVA with one-way analysis of variance was used to determine the mean standard error of the pericyte core area. On single plane pictures, the number of nucleated pericyte cellular bodies was counted and divided by the image's islet surface or exocrine tissue surface (n=3-5 mice per condition, mean SEM, one-way ANOVA). (D) No statistical significance can be found in the results.As previously shown in (33), clamping hyperglycaemia generated by anesthesia (Figure 2B) in HFD-fed mice. Islets, on the other hand, showed an increase in the expression of hypoxia-responsive genes, including as Hif1a and Glut1 (Slc2a1) (Figure 2C)

Optogenetic stimulation may alter the response of Islet Pericytes to HFD.

Cre-dependent expression of the blue-light sensitive cation channel ChR2 in NG2-Cre mice allowed functional probing of pericyte activity in anesthetized mice's intact pancreas. Comparing NG2DsRed and NG2-cre x ROSA26-ChR2tdTomato mice, it was found that the distribution of NG2-ChR2 cells in the islets was comparable in both groups (Figure 3A), and that certain cells in the NG2-ChR2 group expressed PBGFRb and aSMA, as was predicted (Figure S3A). To begin, we looked at changes in islet pericyte shape after HFD diet. Because of the broad coverage of NG2DsRed cells in islet capillaries, we chose NG2DsRed-expressing animals (16, 30, 37). (16, 17). A portion of the NG2DsRed cells also expressed the contractile smooth muscle actin protein (aSMA), consistent with prior findings that characterized the diverse nature of the pericyte population in islets (16). (16, 17). Ins1, Ins2, and Gck gene expression were altered in male NG2-ChR2 animals given a high-fat diet (HFD) for 16 weeks, leading to obesity, hyperglycemia, glucose intolerance, insulin resistance, and faulty glucose-stimulated insulin release (GSIS) (Figure S1). Using optic fibers (l = 473 nm, 1 Hz, 150 ms pulses), laser stimulation was applied to islets (Figure 3B) or exocrine tissue locations while blood flow was measured, as

Indicated (33). When the laser was turned off, the RBC velocity returned to normal (Figures 3B, C), supporting the theory that pericytes regulate islet blood flow (16, 17). (Video S2). NG2-positive pericytes expressed ChR2 in the exocrine tissue, hence laser stimulation impacted RBC velocity in the exocrine tissue as well as the acinar tissue (Video S2). There was no change in blood flow when optogenetic stimulation was applied in another pancreatic lobe, barring effects of a very broad scale (data not shown)

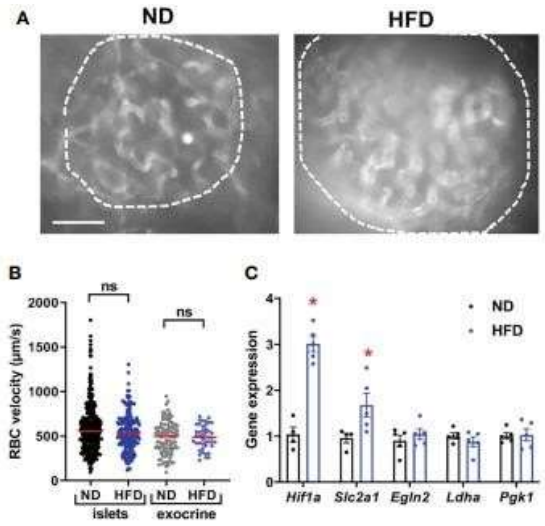

FIGURE 2: ***Following an HFD, basal islet blood flow is unaffected by hypoxia. An islet in a mouse given either a normal diet (ND) or a high-fat diet (HFD) is shown in still pictures from an in vivo video of blood flow (See also Video S1) At a resolution of around 50 nanometers. D2-dextran was used to mark vessel parenchyma. Circumnavigation of Islets In both non-HFD-fed and HFD-fed mice, we measured the velocity of red blood cells (RBCs). A one-way ANOVA was used to analyze the data (n=36 mice/condition, 5-10 vessels/mouse). (C) RT-qPCR was used to evaluate hypoxia markers in islets from mice given a normal diet (ND) and a high-fat diet (HFD). Ppia, Aldo3, Mrlp32, and Tbp Ct values were used to standardize the data, and the results are shown as a fold increase over the ND-fed control. A MannWhitney test was used to analyze the data (n=4-5 mice/group, Mann-Whitney). A significance level of less than or equal to 0.05 is considered to be statistically significant.***

ChR2 deficient control littermates showed no effect of optogenetic activation on blood flow (Figure 3C). When compared to baseline settings, the laser pulse length and strength were optimized to reduce blood flow by 50 percent or more (Figures S3B, C). Mean capillary diameter decreased by 7% (or 0.5 m) in mice with NG2-ChR2 mutations, which was related with a reduction in blood flow (Figure S3D). In islets treated with HFD (Figure 3D), NG2-ChR2 cells remained (Figure 3E), but their sensitivity to laser stimulation was changed (Video S3). RBC velocities were reduced by laser stimulation, but the impact was not immediate and could only be reversed by stopping the light (Figure 3E). In addition, when laser stimulation was turned off, the rise in blood flow velocity seen in islets from HFD-treated rats was substantially less evident (Figure 3E). Animals given either a normal or an HFD did not exhibit these alterations in the exocrine compartment pericytes, indicating that they were exclusive to the islet pericytes (Figure 3F). As a result of HFD therapy, there seems to be a decrease in the sensitivity of islet pericytes to optogenetic activation.

HFD-Induced Alterations in the Expression of Pericyte Markers and Contractile Protein Genes

Genes coding for pericyte markers and contractile proteins were examined in islets exposed to HFD in order to better understand the islet's adaptive response to HFD. Transcriptomic study of isolated brain pericytes (46), which has previously identified indicators of pericytes, showed no significant changes in islets after HFD feeding for these markers of pericytes (Figure 4A). For this reason, we evaluated the expression levels of genes known to be present in mural cells that encoded for proteins that are involved in the contraction of vascular smooth muscle cells (46), and so might be implicated in the dynamics of blood vessels. HFD increased the expression of all genes examined, however only Mylk, Gucy1a3 and Tagln attained significance (Figure 4B).

DISCUSSION

During T2D pathogenesis, the islet vascular network serves as both a support system for beta cells and a pathogenic factor (1). To better understand the effects of high-fat diet on the function of the islet pericyte in mice with T2D, we looked at recent studies showing that islet pericytes are critical for beta cell function, local blood flow regulation, and adequate glucose homeostasis (8, 11, 16, 17) and are morphologically altered in both humans and rodents during T2D (16, 23, 28). Basal local blood flow was unaffected by HFD, despite increased pericyte density in the pancreas. In contrast, islet pericyte responses to optogenetic stimulation were hindered, even when islets expressed genes for proteins implicated in cellular contraction. Hence, we present the first evidence that HFD affects native pancreatic islet pericyte responses in anesthetized mice, which may contribute to T2D pathophysiology via insufficient adaptation of blood supply to increasing islet metabolic demand.

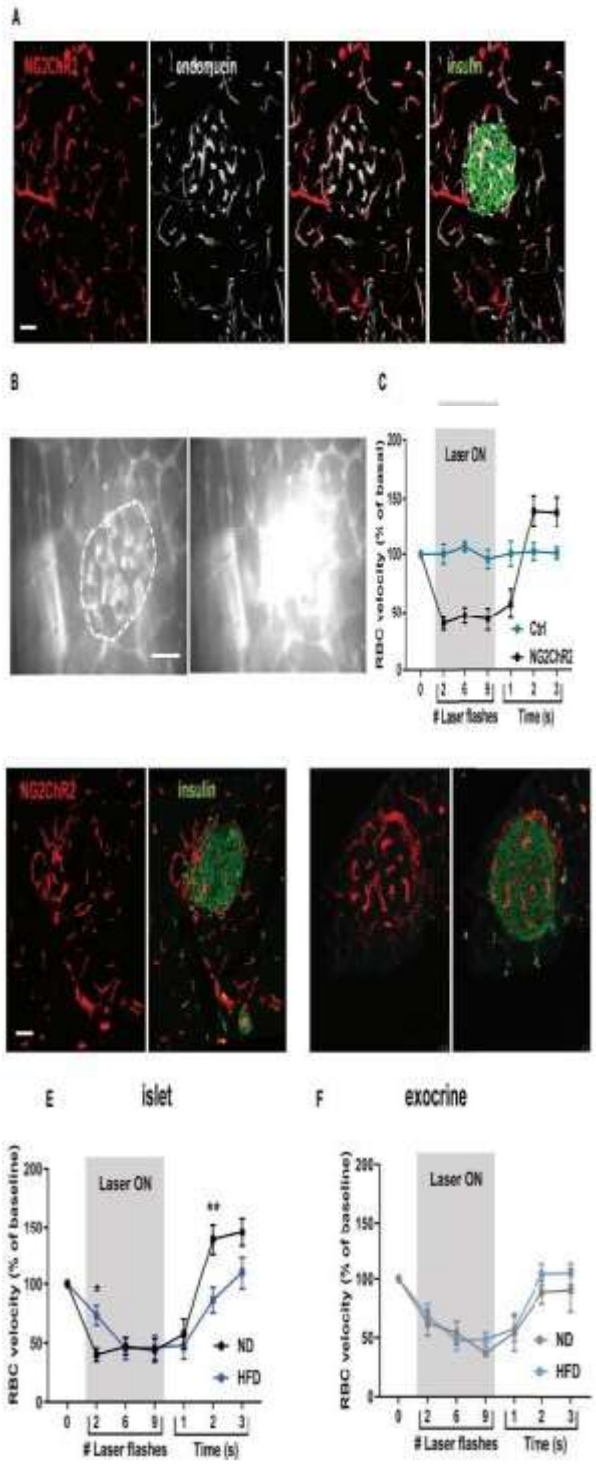

FIGURE 3Pericytes in the pancreas may be stimulated using optogenetics to detect changes in function after a high-fat diet. A confocal picture of an NG2ChR2 mouse pancreatic islet (scale: 50 m, 22 m Z-projection; red: NG2ChR2, green: insulin, white: endomucin) is shown. Still pictures from an in vivo video demonstrating changes in blood flow after laser stimulation of an islet (473 nm, 150 ms, 1 Hz, 200 m fiber at 0.05, **P 0.01; see figure B for details).

Islet capillaries are lined by a varied population of cells known as pericytes. Pericytes express the NG2 and PDGFRb markers, as well as a small percentage of aSMA, as previously demonstrated (16). (16). Notably, NG2 is present in the majority of aSMA pericytes (16). It is possible to tell pericytes apart from arteriolar smooth muscle cells by their morphology, as well as the expression of aSMA and NG2 (37, 47, 48). Following 16 weeks of HFD, pericytes in the islets of rats with insulin resistance and type 2 diabetes (23, 28) were dramatically increased. The changes in morphology were accompanied by a decrease in the number of chromosomes.

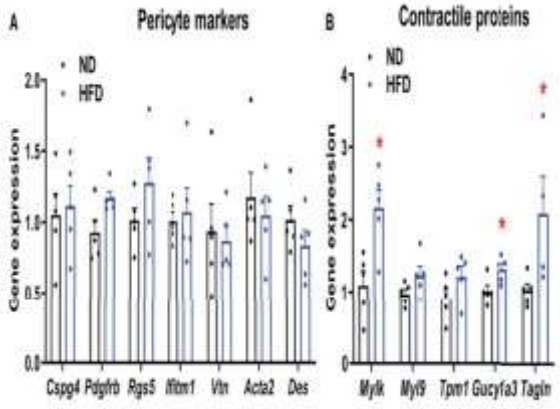

FIGURE 4 | Expression of pericyte and contractile markers in islets from normal diet (ND) and high-fat diet (HFD) fed mice measured by RT-qPCR. Gene expression was measured on islets isolated from 4-5 separate mice/group. Results were normalized by the geometric mean of Ppia, Aldo3, Mrlp32 and Tbp. Ct values and expressed as fold increase relative to ND-fed control. (A) Expression of pericyte markers in islets from normal diet

(ND) and high-fat diet (HFD) fed mice measured by RT-qPCR.

There was no discernible shift in facial expression. A Mann-Whitney test was used to analyze the data (n=4-5 mice/group, Mann-Whitney). B) RT-qPCR analysis of gene expression of contractile protein markers in islets from ND and HFD-fed mice. Mean SEM (n = 4-5 mice/group, Mann-Whitney) data is shown. No statistically significant decrease in the number of pericytes on the human islet surface throughout the evolution of type 2 diabetes (T2D) (16). This genetic model of diabetes exhibits a greater increase in the width of the islet capillaries (by 128%) as well as vascular dilatation in the islets, albeit to a lower degree than the ob/ob mice (23). As a result, baseline RBC velocity in islet capillaries of HFD-fed mice remained unaffected. Interestingly, HFD mice did not have any more stalled vessels, indicating that the distribution of constrictiondilation is more variable. Microsphere measurements of islet blood flow in islets of HFDfed mice failed to identify variations in islet blood flow after correcting for differences in islet volume, on the other hand (49). In contrast, in ob/ob mice, RBC velocity in islets increased by 37%, although this might be accounted by the difference in vessel dilation

between the two models (23). Obesity in humans is thought to occur only in the rarest of cases of leptin insufficiency, and this is not the case in the ob/ob model (50). Because RBCs are so massive in comparison to capillary lumen, even slight changes in capillary width in organs like the brain cause significant reductions in RBC velocity or halting (51). There are, however, little data on how capillary dilation affects blood flow. Since flow changes might occur at varying degrees in various organs due to variable contributions from pericytes and other upstream regulating systems, it's difficult for scientists and engineers to anticipate how much an increase in channel width can boost flow detection. Anesthesia has been shown to cause severe hyperglycemia (33), which hinders measurements of RBC velocities under baseline glucose levels and/or affects upstream processes of islet blood flow control. The effects of islet vessel dilatation on blood flow under physiological settings would need more research. Hif1a and Glut1 (Slc2a1) were increased despite stable blood flow. Hypoxia in beta cells from diabetic islets may be caused by beta cell hyperplasia (52) and oxygen consumption increased by glucose (53, 54). Chronic hyperglycemia may cause islets to become hypoxic, regardless of changes in islet blood flow. The buildup of extracellular matrix, the thickening of the vascular basement membrane, and the fibrosis associated with T2D (20, 21, 28) may all affect nutrition and gas exchanges, although it is not yet clear whether these changes occur after HFD eating. To be sure that HFD-induced hypoxia in beta cells is real, further research is needed. Signaling substances released by neighboring cells are linked to pericyte contraction and relaxation (6, 16). ATP-derived adenosine has been proven to calm pericytes when released with insulin (16). Sympathetic nerve impulses, on the other hand, tighten islet pericytes (16). It is also possible that endothelial-derived vasoactive signals generated by local oxygen levels alter pericyte activity at least in the brain and may possibly be implicated in islets. Pericytes and other NG2-expressing cells respond electrically to optogenetic activation because intracellular calcium levels (16) control cell contractility (47, 48, 51, 55). ChR2 was activated using a 200 m diameter fiber optic, however we can't rule out any unintended effects on smooth muscle cells. A notable finding was that the activity of pericytes was decreased in vivo by optogenetic activation, which is consistent with prior results (16, 17). As soon as the laser stimulation was stopped, the blood flow returned to normal, ruling out any local heating effects or injury. However, despite the relatively slight reductions in channel diameter, this is likely enough to cause significant reductions in blood flow, given that the sizes of RBC and capillary lumens are nearly identical (50%). When islet pericytes were stimulated using optogenetics, they showed delayed alterations in blood flow and a reduced ability to restore blood flow after the end of laser illumination. Pericyte marker gene expression remained stable in islets after HFD, indicating that the number of pericytes has not decreased significantly. HFD altered the expression of many genes involved in the contractile machinery, hence this finding is more likely due to a reduced pericyte contractile response (46). We can't rule out the possibility that pericyte hypertrophy is connected to variations in contractile gene expression. If these alterations are particular to islet pericytes (and not detected in acinar pericytes for example), they must be examined further. Myofibroblasts and pancreatic stellate cells, two additional cells that produce contractile proteins, are also activated in T2D. (57). Future scRNAseq/snRNA-seq studies might reveal how metabolic stress affects distinct pancreatic pericyte populations and contractile elements in different ways. Our findings show that the islet's adaptive response to HFD fails to sustain pericyte activity when taken as a whole. It's still unclear how HFD-induced alterations in pericyte activity affect islet pericyte responses to endogenous substances like adenosine and adrenergic receptor agonists. Summary: We demonstrate that metabolic stress affects the shape and activity of islet pericytes in the intact pancreas of mice utilizing optogenetic stimulation of islet pericytes. As a result of these research, a previously unknown role in the development of vascular problems and islet failure in people with type 2 diabetes has been identified.

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