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Pancreatic islet response to hyperglycemia is dependent on peroxisome proliferator-activated receptor alpha (PPARα)

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Abstract This study tests the hypothesis that islet peroxisome proliferator-activated receptor alpha (PPARα) influences insulin secretion. Freshly isolated islets of normoglycemic PPARα-null mice display no major alteration of glucose-stimulated insulin release. However, after 24 h of culture in high glucose, PPARα-null islets exhibit elevated basal insulin secretion and fail to increase insulin mRNA. 24-h culture with palmitate replicates this phenotype in wild-type islets. The data suggest that PPARα is needed to ensure appropriate insulin secretory response in situation of short-term hyperglycemia, likely by maintaining islet lipid homeostasis. As such, islet PPARα could contribute to delay the progression of type 2 diabetes.

Keywords: Insulin secretion; High-fat diet; Fatty acid

1. Introduction

The peroxisome proliferator-activated receptor alpha (PPARα) is a ligand-activated nuclear transcription factor that upregulates genes of the FA β-oxidation pathways in various tissues [1,2]. A series of recent studies show that PPARα is a major determinant of FA oxidation in rodent islets and INS β-cells [3–8]. As such, PPARα has the potential to influence islet lipid content and, in turn, insulin release. To address the role of PPARα in β-cell secretory function, we have used the PPARα-null mouse model. Our initial hypothesis was that PPARα-deficiency would lead to lipid accumulation in the islet and impair insulin secretion. Experiments showing that glucose-stimulated insulin secretion (GSIS) was not altered in freshly isolated islets from C57BL/6N PPARα-null mice appeared to disprove this hypothesis [9]. At variance with these observations, Gremlich et al. [8] reported that GSIS is enhanced in islets of Sv129 PPARα-null mice, suggesting that islet PPARα controls negatively insulin release. Accordingly, overexpression of PPARα in INS β-cell causes a significant reduction in GSIS [7]. However, the finding that PPARα is profoundly downregulated in islets of type 2 diabetic Zucker fatty rats is at odds with a negative effect of PPARα on insulin secretion [3]. These observations do not allow a clear-cut conclusion on whether and how PPARα affects β-cell secretory function. This prompted us to reevaluate the capacity of PPARα-null islets to produce insulin, in situation of normal or altered glucose homeostasis.

2. Materials and methods

2.1. Animals

This study was conducted according to the Guidelines for the Care and Use of Experimental Animals. Male PPARα-null mice on either pure Sv129 [10] or 10 generations backcrossed C57BL/6N [11] genetic backgrounds were used with similar results. Mice were maintained under a constant light–dark cycle (light from 7:00 am to 7:00 pm) and received a standard diet (UAR AO4, Epinay/Seine, France) or a high-fat diet containing hydrogenated coconut oil (29%, w/w) for 22 weeks [12]. Blood samples were obtained from the orbital sinus between 9:00 and 10:00 am. Serum was separated and stored at −20 °C until use.

2.2. Serum assays

Plasma insulin was determined using an ELISA kit (Eurobio, Courtaboeuf, France). Leptin and adiponectin plasma levels were measured by radio-immunoassay with commercial kits from Linco Research (St. Louis, MO, USA). Blood glucose was determined by a glucose analyzer (Beckman Coulter, Fullerton, CA, USA).

2.3. Islet isolation and static incubations

Following pancreas digestion by intraductal injection of collagenase, isolated islets were purified by double-hand picking and incubated in 1-h static incubation with 2.8 (basal) or 16.7 mM glucose [13]. Islets from 1 to 2 mice of each genotype were used per experiment. Insulin concentrations in the medium were determined by radio-immunoassay (SB INS 15, CIS Bio International, Gif/Yvette, France).

2.4. Islet culture

After an overnight culture in RPMI 1640 containing 10% fetal calf serum, 11.1 mM glucose and antibiotics, islets were resuspended in fresh media and incubated in RPMI containing 2.8, 16.7 mM glucose or 16.7 mM glucose with palmitate (0.5 mM) at a molar ratio of palmitate to bovine serum albumin of 5:1 [14]. After 24-h of culture, islets were incubated in 1-h static incubation as above.

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2.5. RT-PCR determination of insulin mRNA

Total RNA was extracted from 80 to 120 cultured islets by the guanidinium thiocyanate method [15]. First-strand cDNA was reverse transcribed from total RNA using random hexamers as primers, according to the MMLV first-strand cDNA synthesis protocol (Promega, Lyon, France). Relative quantification of cDNA was performed by real-time quantitative PCR, using the Taqman probe approach, on a Light Cycler instrument (Roche Diagnostics, Meylan, France). Insulin primers and probe were as follows: Insulin Reverse: 5′ CTC CAG TGC CAA GGT CTG AA 3′; Insulin Forward: 5′ GTG GCT TCT TCT ACA CAC CCA T 3′; Insulin Probe: 5′ TTG TGC CAC TTG TGG GTC CTC CAC 3′. PCR was performed for 45 cycles with 10 s at 95 °C, 10 s at 60 °C and 10 s at 72 °C. 18 s rRNA was quantified for normalization.

2.6. Statistical analysis

Data are shown as mean ± S.E.M. Comparison between groups were performed by Student's t test or, for multiple comparisons, one-way ANOVA with Tukey's post testing. A difference at $P < 0.05$ was considered statistically significant.

3. Results

Islet function was analyzed in both C57BL/6N and Sv129 PPARα-null mice with similar results (data not shown). PPARα-deficiency did not significantly alter basal or GSIS in freshly isolated islets (Fig. 1). Addition of 1 mM palmitate amplified GSIS by 2-fold in both wild-type (WT) and PPARα-null islets, indicating that PPARα signaling is not required for acute stimulatory effect of FA on GSIS. Activation of the phospholipase C pathway by carbachol also potentiated GSIS to the same extend (×4) in both genotypes. By contrast, GSIS potentiation by 3-isobutyl 1-methylxanthine (IBMX) that increases cellular cAMP through adenylate cyclase activation, was less efficient in PPARα-null islets (×4) than in WT islets (×7). Further experiments are needed to determine whether activation of PPARα by PKA [16] is required for the full effect of IBMX on insulin release.

To test insulin secretory response of PPARα-null islets in situation of altered glucose homeostasis, mice were fed a high-fat diet. This nutritional challenge is known to induce peripheral insulin resistance and compensatory increase in insulin release.

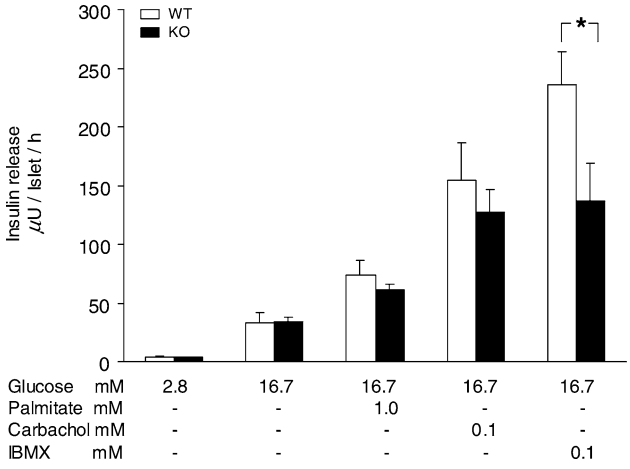

Fig. 1. Insulin secretion in freshly isolated islets from chow-fed WT and PPARα-null (KO) mice. Results are means ± S.E.M. of five to eight separate incubations. Insulin release was significantly higher than at 2.8 mM glucose for each treatment whatever the PPARα genotype ($P < 0.05$ by paired Student's t test). Addition of palmitate, carbachol or IBMX significantly potentiated insulin release at 16.7 mM glucose in both groups ($P < 0.05$ by paired Student's t test). $^{*}P < 0.05$ versus WT by Student's t test.

High-fat feeding enhanced GSIS (×3) in islets from WT mice but was without effect in PPARα-null mice (Fig. 2). Although both WT and PPARα-null mice responded to high-fat by increasing adiposity, as indicated by elevation of plasma leptin, high-fat feeding failed to increase glucose and insulin circulating levels in PPARα-null mice (Table 1). Moreover, adiponectinemia was reduced by twice in hyperinsulinemic WT mice and unchanged in normoinsulinemic high-fat fed PPARα-null mice. These data indicate that PPARα-null mice do not develop diet-induced insulin resistance, a situation likely to preclude islet compensatory increase in insulin release.

Thus, to assess the impact of PPARα deletion under conditions of hyperglycemia, islets were cultured for 24 h in high or low glucose. In low glucose, WT and PPARα-null islets displayed similar rates of insulin secretion (Fig. 3A), with a secre-

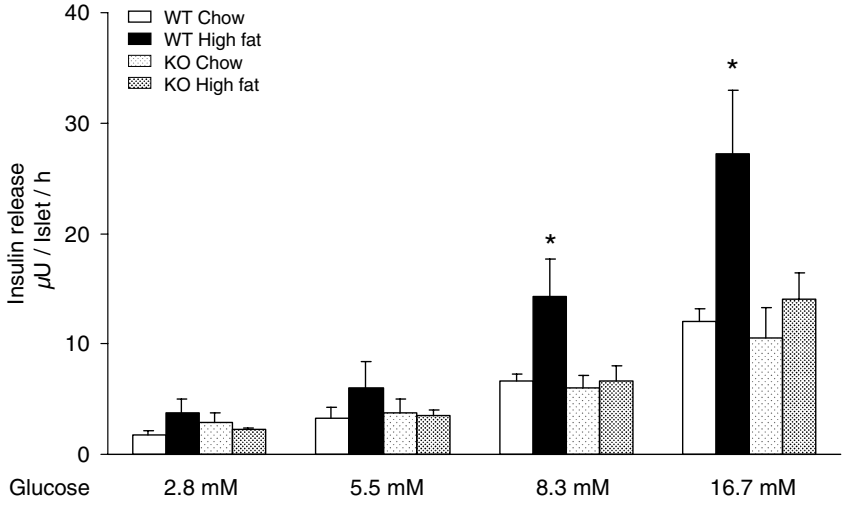

Fig. 2. Effect of high-fat feeding on insulin secretion in freshly isolated islets from WT and PPARα-null (KO) mice. Results are means ± S.E.M. of seven separate incubations. Insulin release at 16.7 mM was significantly higher than at 2.8 mM glucose whatever the diet and the PPARα genotype ($P < 0.05$ by one-way ANOVA). $^{*}P < 0.05$ versus all other bars by one-way ANOVA.

Table 1
Effect of 22 weeks of high-fat feeding in Sv129 WT and PPARα-null mice

	Wild-type mice		PPARα-null mice	
	Standard diet ($n = 9$)	High-fat diet ($n = 9$)	Standard diet ($n = 8$)	High-fat diet ($n = 9$)
Body weight (g)	30.0 ± 0.64	33.7 ± 0.81[b]	30.2 ± 0.83	29.2 ± 0.71[a]
Glucose (mmol/l)	6.9 ± 0.24	7.8 ± 0.35[b]	6.9 ± 0.37	4.4 ± 0.32[a,b]
Insulin (pmol/l)	52 ± 5.4	132 ± 28.1[b]	78 ± 9.0[a]	81 ± 14.8
Leptin (ng/ml)	3.5 ± 0.26	7.2 ± 1.49[b]	4.7 ± 0.77	8.8 ± 1.30[b]
Adiponectin (μg/ml)	33.8 ± 3.84	13.8 ± 3.60[b]	28.0 ± 2.37	26.2 ± 4.13[a]

Data are means ± S.E.M.
[a] $P < 0.05$ versus WT.
[b] $P < 0.05$ versus chow diet by Student's t test.

tion index of 1.8 times basal (Fig. 3B). In WT islets, exposurle to high glucose increased insulin secretion index up to 10 times basal, due to elevated GSIS with no change in basal insulin release. In PPARα-null islets, however, although GSIS increased to the same level as in WT islets, culture in high glucose increased basal insulin secretion, resulting in a 3-fold reduction of secretion index. Similar to PPARα-deficiency, addition of palmitate to the high glucose medium increased basal insulin secretion in WT islets, thereby reducing insulin secretion index to a value similar as in PPARα-null islets. Of note, palmitate was without significant effect as compared to glucose alone in PPARα-null islets.

The regulation of insulin gene expression was analyzed after 24-h of culture in low or high glucose, without or with palmitate. In WT islets, insulin mRNA level was markedly increased (×6) by exposure to high glucose and reduced 4-fold by palmitate, thereby following a closely similar pattern of change as insulin secretion index. This regulation was totally blunted in PPARα-null islets (Fig. 4).

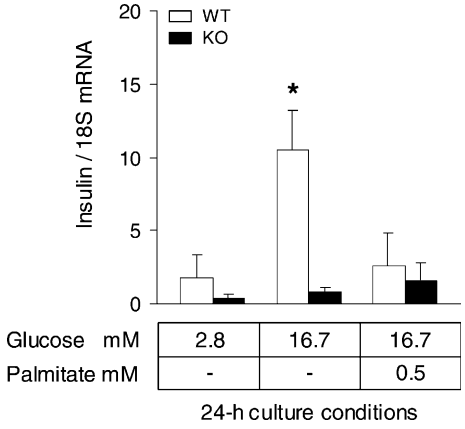

Fig. 4. Insulin gene expression in 24-h cultured islets from WT and PPARα-null (KO) mice. Insulin mRNA was measured in islets cultured for 24-h in presence of 2.8 mM glucose ($n = 4$), 16.7 mM glucose ($n = 5$) or 16.7 mM glucose plus 0.5 mM palmitate ($n = 4$). Results are means ± S.E.M. $^{*}P < 0.05$ versus all other bars by one-way ANOVA.

4. Discussion

The lack of major alteration of insulin release in PPARα-null islets suggests that PPARα is unlikely to play a major role in β-cell insulin secretory function in normal, insulin sensitive mice. However, this does not exclude a modulatory role

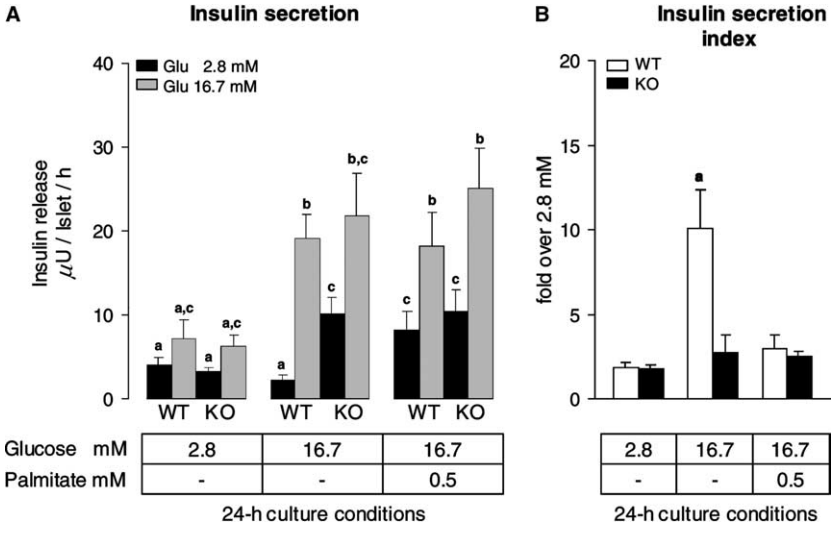

Fig. 3. Effect of 24-h culture in low or high glucose without or with palmitate, on insulin secretion in islets from WT and PPARα-null (KO) mice. (A) Basal (2.8 mM) and glucose induced (16.7 mM) insulin secretion in 1-h incubation of islets cultured in 2.8 mM ($n = 3$), 16.7 mM glucose ($n = 5$) or 16.7 mM glucose plus 0.5 mM palmitate ($n = 5$). (B) Insulin secretion index calculated as the fold stimulation of insulin release induced by 1-h incubation in 16.7 over 2.8 mM glucose. Results are means ± S.E.M. Bars with different letters are significantly different ($P < 0.05$ by one-way ANOVA).

for PPARα under conditions of altered glucose homeostasis. High-fat feeding is known to promote islet hypertrophy in response to increased endogenous demand for insulin production [17], although enhanced insulin secretion is not always observed ex vivo [9,18,19]. Here, GSIS increased 3-fold in islets of high-fat fed Sv129 WT mice but not in PPARα-null mice. These observations are surprising, since it was anticipated that high-fat feeding would favor excessive lipid accumulation in PPARα-null islets and impair GSIS. The most likely explanation is that, since PPARα-null mice are protected from diet-induced insulin resistance [9] (present study), the compensatory changes that normally occur in islets under high-fat feeding did not take place in PPARα-null mice. This prompted us to examine the response of PPARα-null islets to elevated glucose levels in vitro, in the absence of the confounding effect of difference in insulin sensitivity between both genotypes.

We choose to culture islets for 24 h in high glucose to reproduce a situation of short-term hyperglycemia. Our data show that PPARα is needed to ensure correct insulin secretory response in islets exposed to elevated glucose. In normal islets, this adaptive process relied on increased GSIS with no change in basal insulin release. In absence of PPARα, however, elevation of basal insulin secretion markedly reduced the amplitude of insulin response. A similar increase in insulin secretion at low glucose was produced by exogenous palmitate in WT islets, in agreement with previous observations in rat islets [20]. Moreover, the effects of palmitate and PPARα deficiency were not additive, suggesting a common mechanism. Studies by the group of Leahy have shown that 24 h of culture with palmitate increased hexokinase activity in rat islets, by lowering the concentration of its allosteric inhibitor, glucose-6-phosphate [20–22]. As a result, the kinetics of glucose entry into the metabolic pathway is altered, leading to increased insulin secretion at low glucose concentration. Islet PPARα could contribute to minor this lipid-dependent left-shift of glucose concentration/insulin secretion relationship.

Our data further show that PPARα is needed for the induction of insulin mRNA, which is part of the β-cell response to hyperglycemia [23]. The similar inhibitory effect of PPARα deficiency and palmitate suggests that lipid molecule(s) mediate insulin gene downregulation in PPARα-null islets exposed to high glucose. It was recently shown that palmitate inhibition of insulin gene expression is mediated at the transcriptional level via ceramide [24]. This raises the hypothesis that induction of insulin gene by hyperglycemia requires a PPARα-dependent mechanism to lower islet ceramide. Interestingly, PPARα activation reduces neutral sphingomyelinase activity in primary human macrophages, suggesting that PPARα might interfere negatively with the production of ceramide [25].

The question arises whether activation of PPARα signaling ameliorates β-cell function in insulin-resistant states. Amelioration of functional and morphometric parameters of pancreatic islets in insulin resistant rodents treated with fibrates supports this hypothesis [19,26,27]. However, since fibrates enhance whole body insulin sensitivity [26,28,29], this effect, by itself, might be sufficient to ameliorate β-cell sensitivity to glucose [30]. Thus, it is not clear whether beneficial effects of fibrates result from either peripheral insulin sensitization, direct activation of PPARα signaling in the islets, or both.

In conclusion, PPARα signaling does not appear essential for the control of insulin secretion in normoglycemia, but is needed for the β-cell adaptive response to hyperglycemia. The role of PPARα could be to ensure that lipid products, which remain to be identified, do not jeopardize insulin response. This function of PPARα might be crucial to sustain β-cell secretory capacity during the early phases of type 2 diabetes, when the β-cells are submitted to post-prandial episodes of hyperglycemia and need to implement compensatory changes in the face of insulin resistance to delay the progression to overt diabetes.

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