Physiologic and Pharmacologic Modulation of Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Expression in β-Cells by Peroxisome Proliferator–Activated Receptor (PPAR)-γ Signaling

Possible Mechanism for the GIP Resistance in Type 2 Diabetes

Dhananjay Gupta, Mina Peshavaria, Navjot Monga, Thomas L. Jetton, and Jack L. Leahy

OBJECTIVE—We previously showed that peroxisome proliferator–activated receptor (PPAR)-γ in β-cells regulates *pdx-1* transcription through a functional PPAR response element (PPRE). Gene Bank blast for a homologous nucleotide sequence revealed the same PPRE within the rat glucose-dependent insulinotropic polypeptide receptor (GIP-R) promoter sequence. We investigated the role of PPARγ in GIP-R transcription.

RESEARCH DESIGN AND METHODS—Chromatin immunoprecipitation assay, siRNA, and luciferase gene transcription assay in INS-1 cells were performed. Islet GIP-R expression and immunohistochemistry studies were performed in pancreas-specific PPARγ knockout mice (PANC PPARγ$^{-/-}$), normoglycemic 60% pancreatectomy rats (Px), normoglycemic and hyperglycemic Zucker fatty (ZF) rats, and mouse islets incubated with troglitazone.

RESULTS—In vitro studies of INS-1 cells confirmed that PPAR-γ binds to the putative PPRE sequence and regulates GIP-R transcription. In vivo verification was shown by a 70% reduction in GIP-R protein expression in islets from PANC PPARγ$^{-/-}$ mice and a twofold increase in islets of 14-day post-60% Px Sprague-Dawley rats that hyperexpress β-cell PPARγ. Thiazolidinedione activation (72 h) of this pathway in normal mouse islets caused a threefold increase of GIP-R protein and a doubling of insulin secretion to 16.7 mmol/l glucose/10 nmol/l GIP. Islets from obese normoglycemic ZF rats had twofold increased PPARγ and GIP-R protein levels versus lean rats, with both lowered by two-thirds in ZF rats made hyperglycemic by 60% Px.

CONCLUSIONS—Our studies have shown physiologic and pharmacologic regulation of GIP-R expression in β-cells by PPARγ signaling. Also disruption of this signaling pathway may account for the lowered β-cell GIP-R expression and resulting GIP resistance in type 2 diabetes. ***Diabetes*** **59:1445–1450, 2010**

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Glucose-dependent insulinotropic polypeptide (GIP) is a 42–amino acid incretin hormone that binds to a seven-transmembrane G-protein–coupled receptor (GIP-R) that is expressed in numerous tissues including islet β-cells and α-cells (1,2). Its best-known actions in β-cells are to augment meal-related insulin secretion and over the long-term to increase proinsulin synthesis and β-cell proliferation and survival (3,4). Several downstream signaling pathways from the β-cell GIP-R have been characterized. In contrast, little is known about GIP-R expression. A cAMP response element and SP1 and SP2 transcription factor binding sites are present in the 5′ promoter region, but no physiologic modulators are known (4,5). As such, our understanding of GIP physiology is based solely on regulated GIP secretion and rapid metabolism to modulate its cellular actions. The one exception is the lowered number of β-cell GIP-R in animals (6,7) and humans (8) with type 2 diabetes, and the resulting GIP resistance (9), which results from hyperglycemia through an unknown mechanism (7,10).

Our laboratory has studied the biologic actions of PPARγ in β-cells and shown transcriptional regulation of the prodifferentiation transcription factor Pdx-1 (11,12). As part of our studies, we identified the PPAR response element (PPRE) within the *pdx-1* promoter (12). We now report finding the same PPRE sequence within the rat GIP-R promoter, followed by confirming physiologic and pharmacologic regulation of GIP-R transcription in β-cells by PPARγ. Also, we provide evidence that the lowered β-cell GIP-R expression in hyperglycemic rats may result from impaired PPARγ expression.

RESEARCH DESIGN AND METHODS

Animal models. All protocols were in accordance with the principles of laboratory animal care and were approved by the University of Vermont Institutional Animal Care and Use Committee.

60% pancreatectomy (Px) rats. The 5-week-old male Sprague-Dawley rats, and Zucker fatty (ZF, *fa/fa*) or lean controls (ZL, *fa*/+or +/+), underwent 60% Px or sham Px as previously described (11,13).

PANC PPARγ$^{-/-}$ mice. Mice with PPARγ deficiency restricted to pancreatic epithelium were generated by crossing Pdx-1 Cre mice and mice with two floxed PPARγ alleles as previously detailed (12,14). Controls were littermate Cre negative PPARγ floxed mice.

INS-1 cells. INS-1 (832/13) cells were cultured as previously described (11,12).

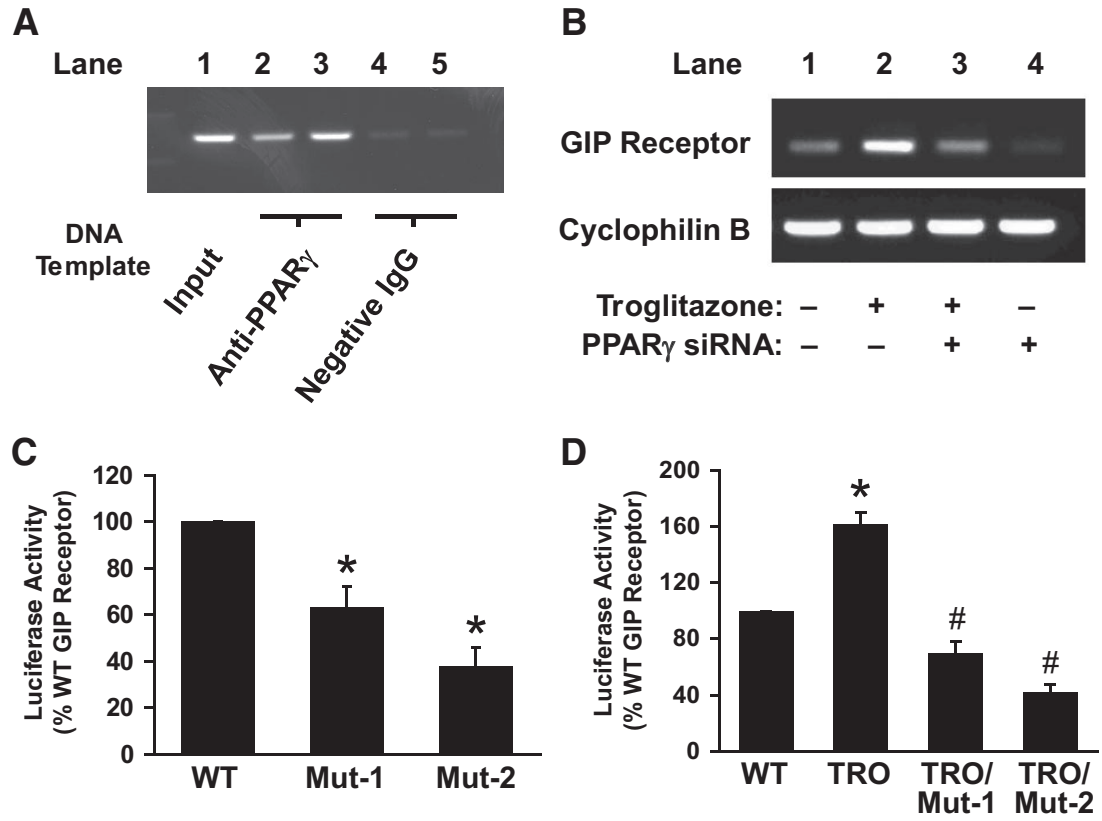

FIG. 1. Experiments in INS-1 cells. *A*: Chromatin immunoprecipitation assay to assess PPARγ binding to the putative PPRE on the *GIP-R* gene. Chromatin fragments (300–500 bp length) were generated. Representative gel showing chromatin preparations from two separate experiments immunoprecipitated with rabbit polyclonal anti-PPARγ (*lanes 2* and *3*) or the negative control nonimmune serum (*lanes 4* and *5*). *Lane 1* is nonimmunoprecipitated DNA. Results show the expected 213-bp PCR product with the anti-PPARγ and input DNA, but not the control serum. *B*: PPARγ siRNA. INS-1 cells underwent transfections with siRNA duplexes against the rat *PPARγ* gene or scrambled siRNA duplexes. Cells were cultured with media that contained 10 μmol/l troglitazone or DMSO for 72 h, and the isolated RNA was assessed for GIP-R mRNA levels by RT-PCR. Representative gels show scrambled siRNA cells cultured with DMSO (*lane 1*), scrambled siRNA cells cultured with troglitazone (*lane 2*), siRNA cells cultured with troglitazone (*lane 3*), and siRNA cells cultured with DMSO (*lane 4*). Cyclophilin B mRNA was used as an internal control. *C* and *D*: Luciferase reporter transcription assay. INS-1 cells were transfected with wild-type or mutated pTAL-PPRE-rat GIP-R vectors, and 24 h post-transfection, the cells were treated with 10 μmol/l troglitazone or DMSO for 24 h. WT = wild-type rat GIP-R PPRE (CCCATG-G-AGGTCA). Mut-1 = mutation of the 5′ DR1 half-site of the rat GIP-R PPRE (AAAATA-G-AGGTCA). Mut-2 = mutation of the 3′ DR2 half-site of the rat GIP-R PPRE (CCCATG-G-ATTTTA). *C* shows the relative basal luciferase activity (DMSO-treated cells) compared with the wild-type rat GIP-R PPRE construct as means ± SEM of three separate experiments. *D* shows the troglitazone treatment effect on luciferase reporter activity of the wild-type and mutated *GIP-R* PPREs. **P* < 0.015 vs. DMSO-cultured wild-type *GIP-R* PPRE cells. #*P* < 0.001 vs. troglitazone cultured wild-type *GIP-R* PPRE cells.

Experimental methods. See the online appendix, available at http://diabetes.diabetesjournals.org/cgi/content/full/db09-1655/DC1.

Statistical analysis. Data are presented as mean ± SEM. Each data point from the animal studies was obtained from an individual rat or mouse. Statistical significance was determined by the unpaired Student's *t* test or two-way ANOVA.

RESULTS

GIP-R promoter PPRE. We previously identified a functional PPRE in the mouse *pdx-1* promoter (12). Gene Bank blast for this nucleotide sequence found a 100% identical sequence in the rat *GIP-R* promoter at positions −871 to −883 from the transcription start site (Gene Bank: AF050667) (supplemental Fig. 1*A*, available in the online appendix). MatInspector software (15) uncovered analogous sequences in the mouse and human GIP-R promoters (supplemental Fig. 1*B*).

INS-1 cell studies. Studies were performed in rat-derived INS-1 cells to confirm functionality of this putative PPRE. PPARγ binding was determined with the chromatin immunoprecipitation assay. Flanking primer pairs for a 213-bp PCR product that included the GIP-R PPRE (schema in supplemental Fig. 2*A*) generated the correct-sized PCR band with input DNA and PPARγ antibody–precipitated DNA, whereas only faint bands were observed with nonimmune serum (Fig. 1*A*). Representative negative and positive controls are shown in supplemental Fig. 2.

PPARγ regulation of GIP-R expression was tested using four pooled siRNA duplexes against PPARγ in INS-1 cells that cause a 75% decrease in PPARγ protein (11). Cells were treated with troglitazone or vehicle for 72 h (Fig. 1*B*). GIP-R mRNA band intensity was markedly lowered in the PPARγ siRNA cells (*lanes 1* and *4*). Troglitazone doubled it in control cells (*lane 2*), whereas the increase was eliminated when troglitazone and the PPARγ siRNA duplexes were used together (*lane 3*).

PPARγ regulation of GIP-R transcription was confirmed with a luciferase reporter gene assay that used a wild-type rat GIP-R promoter fragment and also those containing mutations in the DR1 and DR2 hexamers of the GIP-R PPRE (Mut-1 and Mut-2 fragments), subcloned into the pTAL luciferase reporter vector. The DR1 and DR2 mutations both lowered basal luciferase activity (Mut-1 63 ± 9% of wild-type GIP-R, $P < 0.015$; Mut-2 38 ± 8% of wild-type GIP-R, $P < 0.002$) (Fig. 1*C*). Also, 24-h incubation with

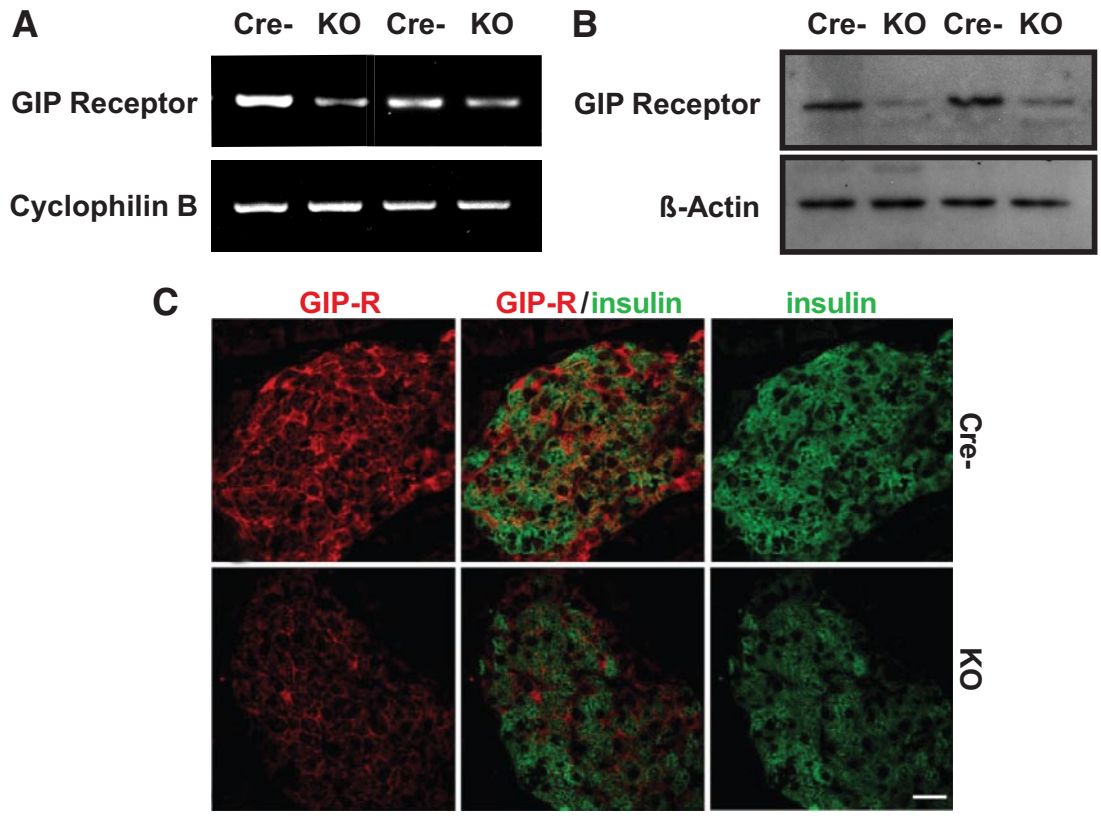

FIG. 2. Islet GIP-R mRNA and protein expression, and pancreas immunostaining for GIP-R, in 8-week-old male PANC PPARγ$^{-/-}$ mice with a pancreas-specific knockout of PPARγ (KO) and littermate floxed control mice (Cre−). Representative gels showing PCR products for islet GIP-R and cyclophilin (*A*) and immunoblots for GIP-R and β-actin from two separate PANC PPARγ$^{-/-}$ and two floxed control mice (*B*) are shown. *C*: Representative islet fields on a pancreas section from a male PANC PPARγ$^{-/-}$ and floxed control mouse stained with rabbit GIP-R antiserum in the *left panels*, costained with insulin antiserum in the *middle panels*, and insulin antiserum alone in the *right panels*. The scale bar is 20 μm. (A high-quality digital representation of this figure is available in the online issue.)

troglitazone (Fig. 1*D*) stimulated expression of the wild-type GIP-R construct (162 ± 8% of vehicle-treated wild-type cells, $P < 0.002$), whereas this effect was absent with both mutations.

In vivo studies. In vivo testing of PPARγ regulation of β-cell GIP-R expression was carried out using PANC PPARγ$^{-/-}$ mice that have a pancreas-specific deletion of PPARγ from a Cre/loxP recombinase system with Cre driven by the *pdx-1* promoter (14). We previously reported that 8-week-old male PANC PPARγ$^{-/-}$ mice are modestly hyperglycemic, with a normal β-cell mass and normal-appearing pancreas histology and islet cytoarchitecture (12). The current studies confirmed the expected defect in GIP-R expression (Fig. 2*A*, mRNA; Fig. 2*B*, protein 29 ± 5% of control, $P < 0.0001$) in isolated islets from these mice. Immunofluorescence studies of pancreas sections showed markedly lowered GIP-R staining in islet β-cells and non–β-cells of PANC PPARγ$^{-/-}$ mice versus control mice (Fig. 2*C*).

Analogous studies were performed in normoglycemic Sprague-Dawley rats 14 days after 60% Px when islet nuclear PPARγ expression is 2.5-fold increased (11). Comparable increases in GIP-R mRNA (Fig. 3*A*) and protein (Fig. 3*B*, 1.9 ± 0.2-fold of sham, $P < 0.02$) were found in Px versus sham rat islets. Also, GIP-R staining intensity was increased in islet β-cells and non–β-cells versus the sham rats (Fig. 3*C*).

Troglitazone studies. Thiazolidinedione (TZD) stimulation of GIP-R expression was tested by incubating normal mouse islets for 72 h with troglitazone or vehicle. Troglitazone caused a near-tripling of the GIP-R protein level (supplemental Figs. 3*A* and *B*, 2.7 ± 0.4-fold of DMSO islets, $P < 0.02$). Also the insulin response to 16.7 mmol/l glucose/10 nmol/l GIP peptide was nearly doubled ($P < 0.05$), whereas insulin responses to 2.8 mmol/l glucose with or without GIP peptide, and to high glucose alone, were unchanged (supplemental Fig. 3*C*).

Hyperglycemic rats. We speculated that impaired PPARγ expression caused the β-cell GIP-R depletion in animal models of type 2 diabetes (6,7). Accordingly, we performed PPARγ and GIP-R Western blots on islet extracts from 3-week postsurgery 60% Px and sham-operated ZF and ZL rats, based on our report that Px ZF rats are hyperglycemic (~15 mmol/l) with the same degree of obesity and serum levels of nonesterified fatty acids and GIP as normoglycemic sham ZF rats (13). Figure 4 shows that islet PPARγ and GIP-R protein levels are doubled in the sham ZF versus sham ZL rats (1.9 ± 0.1-fold, $P < 0.001$; 2.2 ± 0.3-fold, $P < 0.01$, respectively). In contrast, both are lowered by 60% in Px (hyperglycemic) ZF islets versus the sham (normoglycemic) ZF islets (0.7 ± 0.1-fold and 0.8 ± 0.1-fold of sham ZL islets, respectively).

DISCUSSSION

We used in vitro and in vivo techniques to show for the first time that GIP-R transcription in β-cells is regulated by PPARγ. Also, that pharmacologic activation of PPARγ by TZDs induces the same effect resulting in greater GIP potentiation of glucose-induced insulin secretion. These

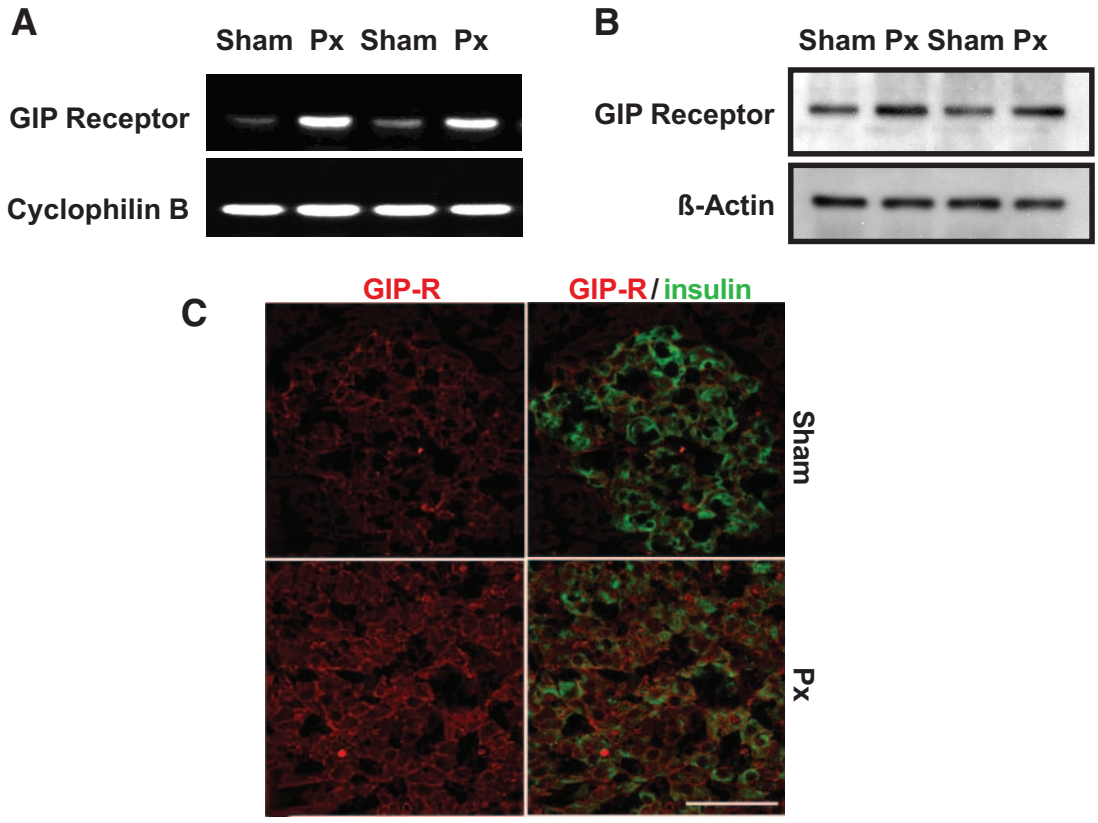

FIG. 3. Islet GIP-R mRNA and protein expression, and pancreas immunostaining for GIP-R, in 14-day postsurgery 60% Px and sham-operated Sprague-Dawley rats. Representative gels showing PCR products for islet GIP-R and cyclophilin (*A*) and immunoblots for GIP-R and β-actin from two separate Px and sham rats (*B*) are shown. *C*: Representative islet fields on pancreas section from a Px rat and a sham-operated rat stained with rabbit GIP-R antiserum in the left panels and costained with insulin antiserum in the right panels. The scale bar is 20 μm. (A high-quality digital representation of this figure is available in the online issue.)

results add to our prior studies of PPARγ signaling in β-cells that showed 40% of adult mouse islet *pdx-1* expression is PPARγ regulated (11,12) by our now finding a second gene with the identical PPRE and functional characteristics.

There are several noteworthy implications to these results. First, Pdx-1 is considered the most important transcription factor in β-cells related to its essential role for normal β-cell function, viability, and compensation capacity (16). Also, studies of incretin receptor knockout mice and in vivo usage of GIP-R peptide agonists have demonstrated a necessary role for GIP in normal mealtime glucose tolerance and insulin secretion (17,18). Clinical trials have found a particularly high success rate of TZDs in pre-diabetes and early type 2 diabetes, with the mechanism believed to be the peripheral insulin sensitization lowering the drive for insulin secretion (so-called "β-cell rest") (19). However, given the importance of the identified PPARγ-regulated genes in β-cells, our results raise the possibility that direct PPARγ-mediated effects on β-cells also account for some of the clinical benefits. Indeed, others have shown a direct effect of TZDs to restore Pdx-1 levels and reduce endoplasmic stress in islets from diabetic rats (20).

Second, there is the possibility we have uncovered an unknown feature of incretin physiology, i.e., variable GIP-R expression, related to our finding increased islet GIP-R expression in two rat models of β-cell compensation from unrelated causes: reduced β-cell mass in 60% Px Sprague-Dawley rats (21) and mutated leptin receptors resulting in obesity, insulin resistance, and hyperlipidemia in ZF rats (13). This shared observation is particularly interesting, since there is no precedence for GIP-R hyperexpression except in the adrenocortical tumors of some individuals with Cushing's syndrome (22). Also, our finding that the GIP-R hyperexpression in both models was paralleled by increased β-cell expression of PPARγ (11; Fig. 4) is consistent with the main conclusions of this study regarding PPARγ regulation of β-cell GIP-R expression. On the other hand, an in vitro study reported PPARα regulates β-cell GIP-R expression and speculated this effect occurs in vivo related to the β-cell fatty acid load (23). This mechanism seems unlikely in the 60% Px Sprague-Dawley rats, since serum triglyceride and free fatty acid levels are unchanged post-Px in lean rats (13,21), plus islet PPARα expression is reduced (13). In contrast, ZF rats are markedly hyperlipidemic (13), making this a potential mechanism. Also the lack of a post-Px increase in PPARγ and GIP-R expression in ZL rats (Fig. 4) may reflect the different times of study—3 weeks post-Px in ZL rats versus 2 weeks post-Px in Sprague-Dawley rats.

The third implication of our results is our speculation that aberrant PPARγ signaling is a new mechanism for the lowered β-cell GIP-R expression and GIP resistance in animal and human type 2 diabetes (6–9). Hyperglycemia causes this effect in animals (7,10), but no mechanistic details are known except for a study that reported accelerated GIP-R degradation in islets cultured at high glucose conditions (24). Figure 4 supports our proposal by showing parallel reductions in islet expression of PPARγ and GIP-R in the hyperglycemic ZF rats. However, Px ZF rats

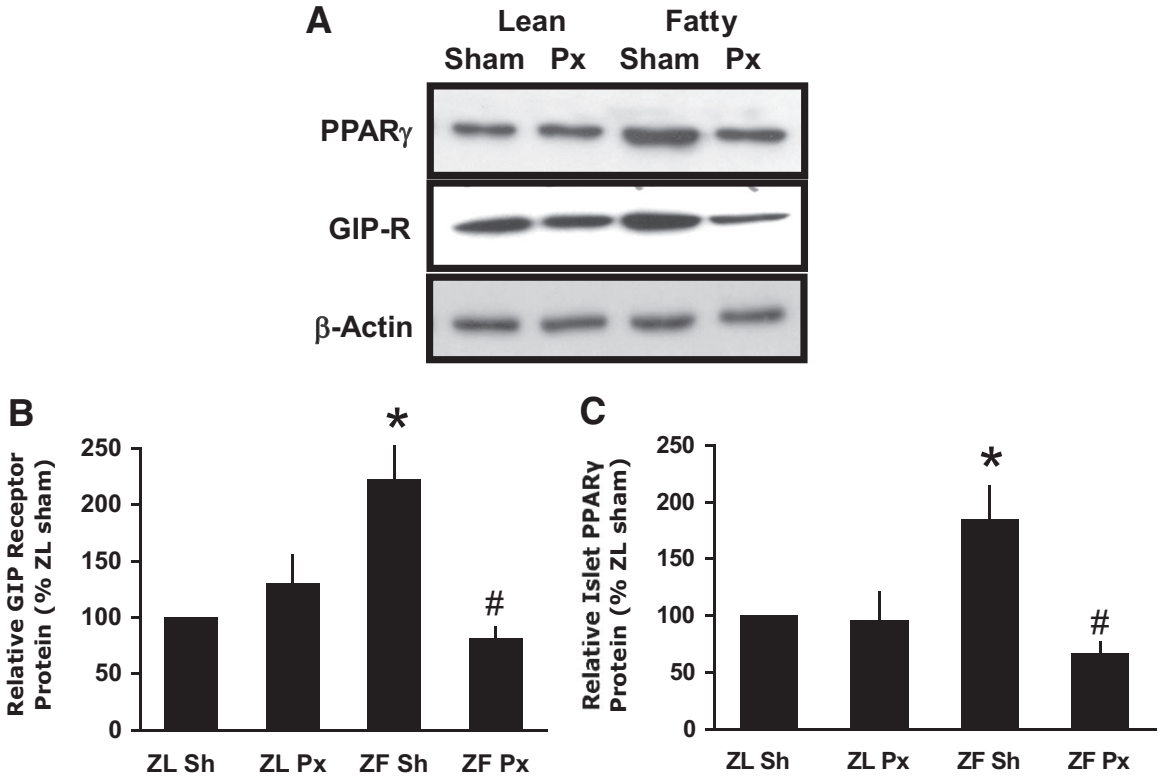

FIG. 4. Islet GIP-R and PPARγ protein expression in Zucker fatty (*fa/fa*) and Zucker lean (*fa/+*, *+/+*) rats 3 weeks post 60% Px or sham-Px surgery. *A*: Representative immunoblots for GIP-R, PPARγ, and β-actin in islet extracts from 60% Px or sham-operated ZF and ZL rats. *B* and *C*: Graphs showing % means ± SEM band intensities for GIP-R and PPARγ, respectively, relative to sham-operated ZL islets using data from four separate experiments. **P* < 0.005 ZF sham vs. ZL sham islets. #*P* < 0.005 ZF sham vs. ZF Px islets.

also have a reduction in islet PPARα mRNA expression (13), so the exact mechanism is unknown. A related issue is the lowered β-cell expression for the other incretin hormone receptor (GLP-1) in animals and humans with type 2 diabetes (7,8). However, the molecular mechanism is likely different from the GIP-R depletion based on the study by Xu et al. (7) that performed 96-h glucose infusions in conscious rats and found islet GLP-1R mRNA levels fell 50%, whereas GIP-R mRNA levels modestly increased, plus they noted the same divergence in 2-day high glucose cultured islets. Also, it is likely that the lowered islet incretin receptor expression in type 2 diabetes is multifactorial, with recent interest in disrupted TCF7L2 signaling (8). Thus, our results suggest that β-cell PPARγ regulation of GIP-R expression is a newly identified feature of incretin (patho)-physiology and TZD therapeutics. Also the lowered islet PPARγ expression in Px ZF rats (glycemia 15 mmol/l) may provide a new understanding why TZD therapy is so powerful in pre-diabetes and early type 2 diabetes as opposed to the more modest efficacy with advanced type 2 diabetes (19,25).

In summary, GIP-R is a newly described PPARγ-regulated gene in β-cells. Expression of both genes is increased in rat models with β-cell adaptation to diverse stimuli. Also, TZDs augment GIP potentiation of glucose-induced insulin secretion through this mechanism. In contrast, this expression system is downregulated in diabetic rats. As such, our studies have uncovered a new mechanism for regulatory control of the β-cell GIP-R expression and may have added a new understanding to incretin (patho)-physiology and TZD therapy.

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No potential conflicts of interest relevant to this article were reported.

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