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The role of peroxisome proliferator-activated receptor γ in pancreatic β cell function and survival: therapeutic implications for the treatment of type 2 diabetes mellitus

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Abstract

The pathogenesis of type 2 diabetes mellitus involves both peripheral insulin resistance and dysfunctional insulin secretion from the pancreatic β cell. Currently, there is intense research focus on delineating the etiologies of pancreatic β cell dysfunction in type 2 diabetes. However, there remains an unmet clinical need to establish therapeutic guidelines and strategies that emphasize the preservation of pancreatic β cell function in at-risk and affected individuals. Thiazolidinediones are orally active agents approved for use in type 2 diabetes and act as agonists of the nuclear hormone receptor PPAR-γ. These drugs improve insulin sensitivity, but there is also a growing appreciation of PPAR-γ actions within the β cell. PPAR-γ has been shown to regulate directly key β cell genes involved in glucose sensing, insulin secretion and insulin gene transcription. Further, pharmacologic PPAR-γ activation has been shown to protect against glucose-, lipid-, cytokine- and islet amyloid polypeptide (lAPP)-induced activation of numerous stress pathways. This article will review the mechanisms by which PPAR-γ activation acts to maintain β cell function and survival in type 2 diabetes mellitus and highlight some of the current controversies in this field.

Keywords

β cell; diabetes mellitus; PPAR-γ agonist

Introduction

Type 2 diabetes mellitus (T2DM) is a disease of disordered glucose homeostasis that affects an estimated 200–250 million individuals worldwide [1]. The pathogenesis of T2DM involves both peripheral insulin resistance and dysfunctional insulin secretion from the pancreatic β cell. Studies documenting the natural history of this disease suggest two roles

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Conflict of Interest

D. G., T. K. and C. E. M. worked together to create an outline for this review article. D. G. and T. K. worked on initial drafts, while C. E. M. was responsible for editing and compiling the final version.
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for the pancreatic β cell [2,3]. The first is that 'at-risk' individuals possess an inherent tendency towards β cell failure. These individuals are therefore predisposed towards the development of diabetes in settings where insulin sensitivity is compromised [4–16]. States of obesity and decreased peripheral insulin sensitivity lead to elevated serum levels of glucose, adipocytokines and free fatty acids as well as other deleterious lipid intermediates [17]. These toxic mediators harm the β cell through several intersecting mechanisms including oxidative stress, mitochondrial dysfunction, epigenetic dysregulation and activation of endoplasmic reticulum (ER) stress pathways [18–21]. While there is a great overlap between many of these processes, the final common pathway that results is β cell dysfunction and death. Thus, the second component of this paradigm is that the altered metabolic milieu of T2DM leads to progressive β cell failure and loss of functional β cell mass over time.

Given this broader and evolving understanding of the role of the β cell in the pathogenesis of T2DM, there is a clinical need to identify treatment strategies and pharmacologic targets that prevent the development of diabetes in genetically or epigenetically 'at-risk' individuals. Further, there is a parallel need to maintain β cell function and mass in affected individuals. Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor γ (PPAR-γ) agonists, were first approved for clinical use in the treatment of T2DM in 1997 [22]. Although these agents have been largely viewed as peripheral insulin-sensitizing agents, there is a growing appreciation for PPAR-γ regulated transcriptional and signalling events within the pancreatic β cell. This article will provide an overview of the mechanisms through which pharmacologic PPAR-γ activation may act to enhance pancreatic β cell homeostasis and highlight some of the current controversies associated with the use of these agents in T2DM.

Pharmacological PPAR-γ Activation and the Preservation of β Cell Function; Controversies in the Field

PPAR-γ (NR1C3) is a member of nuclear hormone receptor superfamily of ligand-activated transcription factors. TZDs are orally active agents that act as high-affinity activators of PPAR-γ [23]. There are currently two TZDs approved for use in type 2 diabetes in the United States: pioglitazone and rosiglitazone. Troglitazone was the first drug in the class approved by the Food and Drug Administration (FDA), but was subsequently withdrawn from the market after several patients developed fulminant hepatic failure [24]. TZD therapy in persons with diabetes has been shown to lower haemoglobin A1c levels, and initial trials showed that TZDs act to enhance peripheral insulin sensitivity in the liver, adipose and skeletal muscle [23,25]. However, the additional role of PPAR-γ-mediated events in the pancreatic β cells has been studied extensively since the confirmation of PPAR-γ expression in rodent and human pancreatic islets [26,27].

Results from several large clinical trials have supported the idea that PPAR-γ agonists, in addition to their known effects on insulin-sensitive tissues, may have complementary benefits in the β cell. A number of studies including the Diabetes Prevention Program (DPP) and Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial have shown that PPAR-γ agonists, when administered to individuals with impaired glucose tolerance (IGT), prevent or delay the onset of T2DM [28,29]. TZD therapy has also been shown to prevent the development of diabetes in individuals with a history of gestational diabetes mellitus (GDM). Those with GDM are considered to be an extremely high-risk population and have nearly a 50% chance of developing permanent diabetes within 5 years of the affected pregnancy [30–32]. Further, A Diabetes Outcome Progression Trial (ADOPT) showed that treatment with rosiglitazone in type 2 diabetes for a median of 4

years was associated with improved glycaemic durability as compared to sulphonylurea or metformin therapy [33].

These and other trials have also shown objective improvements in various measures of β cell function in T2DM. In persons with diabetes, TZDs have been shown to decrease the serum proinsulin to insulin ratio and improve glucose-entrained insulin secretion [34,35]. The proinsulin to insulin ratio is increased in diabetes and reflects dysfunctional processing of the insulin prohormone. An elevated ratio is also a marker of impaired β cell secretory response [36]. TZDs have further been shown to increase the insulin secretion/insulin resistance index as defined by oral glucose tolerance tests (OGTT) and euglycaemic insulin clamp studies. This index is defined as the change in incremental area under the curve (AUC) of plasma insulin during OGTT divided by the incremental AUC of plasma glucose during an OGTT. This ratio is then normalized for changes in insulin resistance, which is determined by euglycaemic clamp. Essentially, an improvement in the insulin secretion/ insulin resistance index implies an improvement in the acute β cell insulin-secretory response to glucose. Because this assessment factors in changes in insulin sensitivity, the improvement in insulin secretion can be attributed directly to improvements in β cell function [37].

The homeostatic model of assessment-%B (HOMA-%B) is a method of mathematical modelling that allows for a surrogate assessment of β cell function during an intravenous glucose tolerance test (IVGTT). Using this method, Wallace et al. showed an improvement in HOMA-%B in subjects with diabetes who were treated with pioglitazone for 3 months [35]. The ADOPT trial further showed a slower rate of decline in HOMA-%B in rosiglitazone-treated subjects compared with those treated with either glyburide or metformin [33].

With regard to those at risk for the development of diabetes, including those with IGT, impaired fasting glucose (IFG) or a history of GDM, TZDs have been shown to produce similar results. Cavaghan and colleagues showed that 12 weeks of troglitazone treatment in individuals with IGT led to improved insulin secretion, when adjusted for insulin sensitivity, and improved β cell sensing during an oscillatory glucose infusion [38]. In a ‘prediabetic’ population, rosiglitazone treatment for 2 years, in the DREAM trial, led to a decreased fasting proinsulin to C-peptide ratio. Further, during OGTT, rosiglitazone-treated individuals manifested an improved insulinogenic index [39]. This measure is similar to the insulin secretion/insulin resistance index performed by Gastaldelli et al. except that insulin resistance was modelled from the homeostatic model of assessment (HOMA) calculation rather than directly measured from an insulin clamp. Finally, in patients with a history of GDM, the TRoglitazone In the Prevention of Diabetes (TRIPOD) and Pioglitazone in Prevention of Diabetes (PIPOD) studies have both shown that TZD use is associated with a stabilization of β cell function, as assessed by the disposition index. This is compared to placebo-treated controls, where worsening function was shown over the same time period [31,32].

The results of key trials, which have directly studied TZD effects on β cell function, are summarized in Table 1. In aggregate, these studies show that TZD use in persons with diabetes and those at risk for diabetes is associated with improvements in β cell secretory response and glucose sensing. Further, in persons with diabetes, TZD use led to improved glycaemic outcomes over time that can be attributed to changes in insulin sensitivity, but also importantly, to improvements in β cell function independent of any change in insulin sensitivity.

Genetic Ablation of PPAR-γ in Pancreatic Islets

In spite of these aforementioned clinical observations, there has been continued controversy over whether PPAR-γ agonists have direct or indirect effects on the pancreatic islet. In part, this debate has been fuelled by conflicting data from rodent models of PPAR-γ ablation. Matsui et al. created a model of total body heterozygous PPAR-γ deletion. Interestingly, these mice were protected from high-fat diet-induced insulin resistance. Whereas peripheral tissues showed decreased triglyceride levels, there was an increase in intraislet triglyceride that led to impaired islet glucose oxidation. Administration of pioglitazone reversed these changes and restored islet function [40].

A pancreatic β cell-specific PPAR-γ knockout model (βγ KO mice) naturally followed and was generated by crossing mice with floxed PPAR-γ gene (PPARG) to mice expressing Cre driven by rat insulin II promoter (RIP-Cre). βγ KO mice displayed significant islet hyperplasia on normal chow diet, but had a blunted response towards β cell mass expansion when challenged with high-fat feeding. Isolated islets from βγ KO mice also exhibited a blunted TZD response towards glucose-stimulated insulin secretion (GSIS) yet normal physiological parameters after high-fat feeding. On the basis of these findings, the authors concluded that PPAR-γ had an inconsequential physiological role in the β cells, and these outcomes led support to the idea that the beneficial effects of PPAR-γ agonists are secondary solely to enhanced peripheral insulin sensitivity [41].

Recently, another pancreatic-specific KO model of PPAR-γ was generated by crossing mice with a floxed *PPARG* gene to mice expressing Cre driven by the pdx-1 promoter (PANC PPAR-γ−/−). Islets from PANC PPAR-γ−/− mice showed normal cytoarchitecture and no hyperplasia. Interestingly, the PANC PPAR-γ−/− mice exhibited glucose intolerance at baseline. Isolated islets show blunted glucose-stimulated insulin secretion as well as downregulation of pdx-1 and GLUT2 expression, with no effect on glucagon levels [42].

The apparent differences between the βγ KO and PANC PPAR-γ−/− mice are not fully understood, but several factors should be considered. First, it is plausible that pdx-1-driven Cre is expressed fairly early during development of the endocrine pancreas as compared to RIP-Cre. This difference may have developmental implications. Further, hypothalamic expression of the RIP-Cre has been described [43], and one could speculate that differences in the expression of PPAR-γ within the hypothalamus between the two models may have affected neuronal regulation of energy homeostasis and glucose metabolism. Although, hypothalamic expression of pdx-1 Cre has not yet been formally reported, pdx-1 is present in neural cells during brain development [44]. There are examples of models that have employed the pdx-1 Cre, which have specifically shown unaltered expression of the floxed gene within the hypothalamus [45,46]. Specifically, Gupta and colleagues show robust expression of PPAR-γ in the hypothalamus of their PANC PPAR-γ−/− model [42]. Notwithstanding this controversy, PPAR-γ immunoreactivity has been observed in a majority of neurons in the arcuate and ventromedial hypothalamic nuclei that control energy homeostasis and glucose metabolism [47]. The neuron-specific deletion of PPAR-γ, however, seems to have no significant effect on normal food intake or body weight on 4 weeks of normal chow. Finally, the RIP-Cre model has been reported to have glucose intolerance at baseline [48,49]; therefore, the findings in the βγ KO model are difficult to interpret. A long-term high-fat feeding or partial pancreatectomy study using the pdx-1 Cre-driven KO mouse model would potentially help to clarify the contribution of PPAR-γ-mediated signalling events in the β cells under stress conditions.

Mechanisms of PPAR-γ Action

Although there have been discrepant results from animal models of PPAR-γ deletion within the islet, a broader understanding of the role of PPAR-γ in the pancreas has been provided by a number of cell-based studies. To interpret these studies, it is useful to review the molecular mechanisms of PPAR-γ action. To function as a transcriptional regulator, PPAR-γ must be ligand activated, undergo heterodimerization with retinoid X receptors (RXRs: NR2B), recruit co-factors and recognize peroxisome proliferator response elements (PPREs) in the 5′ promoter region of a target gene. The consensus sequence for a PPRE consists of two direct repeats consisting of AGGTCA (direct repeat 1 and 2 or DR1 and DR2) separated by a nucleotide, although several variations of this consensus have been described [50]. Within a typical PPRE, the 5′-half is occupied by PPAR-γ, while the 3′-halfis occupied by RXR [51]. A recent comparison of known reported 73 DRl-like PPREs reflects the presence of heterogeneity, while the DR2 core sequence appears to be more highly conserved [52]. Further, stringent binding of RXR on the 3′-half of PPRE is more influential on the binding of PPAR-γ/RXR heterodimer than the ability of PPAR-γ to bind DNA In addition, PPAR-γ has been shown to bind as a homodimer to palindromic sequences separated by three nucleotides [53]. In the absence of ligand, PPAR-γ is bound by a co-repressor and the transcriptional effects are blocked [54].

PPAR-γ is expressed in a variety of tissues, although it is considered to be most abundantly expressed in adipose tissue [55]. However, protein levels of PPAR-γ in both rodent and human islets are comparable to levels observed in adipose tissue [26,56]. PPAR-γ expression in the islet may, however, change in response to environmental or stress conditions. Chronic exposure to high glucose has been shown to decrease PPAR-γ mRNA levels in mouse islets [57]. Further, Moibi et al. showed that PPAR-γ is upregulated 2 weeks after a 60% pancreatectomy procedure in rats. This coincided with a switch from a proliferative to a prodifferentiation state [58].

PPAR-γ Target Genes in the Pancreatic β Cell; Profunction Effects of PPAR-γ Activation

The β cell is the only cell in the body responsible for physiologic insulin secretion, thus it possesses a complement of highly specialized cellular machinery to accomplish the key tasks of glucose sensing and insulin release. Insulin secretion in the pancreatic β cell has been classically ascribed to an ATP-sensitive potassium (K_{ATP}) channel-dependent mechanism. In this model, glucose is taken up into the β cell through the glucose transporter (GLUT) [59]. In the rodent, GLUT2 is the predominant isoform; however, in human β cells, GLUT1 appears to play a more prominent role [60,61]. Upon entry into the β cell, glucose is converted to glucose-6-phosphate by glucokinase. Glucokinase, in contrast to other hexokinase isoforms in other tissue types, has a low affinity (high Km) for glucose, displays co-operativity with respect to glucose and serves as the rate-limiting step for glucose uptake [62]. Glucose-6-phosphate is subsequently converted to pyruvate in the glycolytic pathway, which is then converted to acetyl coenzyme A (CoA) and enters the tricarboxylic acid (TCA) cycle. The TCA cycle produces reducing equivalents and ATP resulting in an increase in the ATP/ADP ratio within the islet. This increase in the ATP/ADP ratio brings about closure of the K_{ATP} channels, leading to membrane depolarization and subsequent activation of voltage-gated Ca^{2+} channels as well as Ca^{2+} influx from the extracellular space and ER [63]. This increase in cytosolic Ca^{2+} ultimately serves to activate insulin granule docking and release from a readily releasable pool of secretory vesicles [64].

GSIS does not occur solely through this KATP-dependent mechanism. There are several alternative metabolic pathways that serve to amplify insulin secretion. These processes have

been reviewed in detail elsewhere and include pyruvate carboxylase-mediated anapleurotic reactions, NADH shuttles and glutamate production from glutamate dehydrogenase [65,66]. In addition, the gut-derived incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) stimulate glucose-dependent insulin secretion through activation of their cognate receptors and subsequent downstream signalling, involving the production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A and guanine nucleotide exchange factors [67].

TZD administration has been shown to enhance glucose sensing and insulin secretion from diabetic rodent and human β cells [34,38,68,69]. With regard to PPAR-γ regulation of these K_{ATP}-independent processes, Jitrapakdee and colleagues showed that PPAR-γ is a direct transcriptional regulator of pyruvate carboxylase in white and brown adipose tissues [70]. This relationship, however, has not been studied directly in the β cell. Further, Gupta and colleagues recently showed a PPRE in the GIP receptor gene and showed, functionally, that this gene was a direct target of PPAR-γ [71].

PPAR-γ is also known to regulate components of the classical KATP-dependent GSIS pathway. The promoters of GLUT2 and glucokinase are reported to have functional PPREs that bind the PPAR-γ/RXRα heterodimer, and PPAR-γ activation leads to transcriptional upregulation of these genes in the β cell [72,73]. Further, the expression of these genes is impaired in rodent models of diabetes [68,74]. Little is known, however, about the regulation of GLUT1 by PPAR-γ in the human β cell. TZDs have been shown to increase expression levels and activity of the GLUT1 transporter in skeletal muscle and adipocytes [75–77].

Insulin secretion and transcription are closely linked in the pancreatic β cell, and insulin gene expression is carefully regulated through a network of interacting transcription factors [78–80]. Pdx-1 is often referred to as the master pancreatic transcription factor and plays a key role in normal pancreatic and β cell development as well as maintenance of the mature β cell phenotype (reviewed in [81]).Homozygous loss ofPdx-1 is associated with pancreatic agenesis, while Pdx-1 haploinsufficiency results in a subtype of the monogenic diabetes disorders: MODY4 or Maturity Onset Diabetes of the Young 4, a disease characterized by impaired insulin secretion and subsequent hyperglycaemia [82–84]. In the mature β cell, Pdx-1 binds the proximal insulin promoter and positively regulates glucose-stimulated insulin transcription [85]. Pdx-1 gene and protein expression are also known to be downregulated in rodent and *in vitro* models of diabetes [74,86,87]. Further, in db/db mice and a rat insulinoma cell line (INS-1) incubated with the ER stress-inducing compound, thapsigargin, the loss of Pdx-1 expression was restored with pioglitazone [68]. A recent report by Gupta and colleagues showed that Pdx-1 is, in fact, a direct target of PPAR-γ in the islet [42].

Pharmacologic PPAR-γ activation in normal and diabetic β cells has been shown to upregulate a number of other genes whose products mediate key aspects of normal function. Chronic administration of pioglitazone to db/db mice led to upregulation of the gene encoding Nkx6.1, a protein that regulates insulin transcription, secretion and replication [88]. More acute treatment of INS-1 cells with troglitazone showed the same results [58]. Other genes similarly affected included NeuroD1, Kcnj11, Irs1 and the insulin gene [68,89]. However, to date, these genes have not been investigated or validated as direct PPAR-γ targets.

Prosurvival Effects of PPAR-γ Activation in Diabetic β Cells

In addition to the profunction effects described earlier, PPAR-γ activation in the pancreatic β cell has been associated with a variety of prosurvival effects arising within the context of

T2DM. There are a number of toxic mediators in T2DM that result in activation of stress pathways. These include elevated glucose, free fatty acids, proinflammatory cytokines and islet amyloid polypeptide (IAPP). These factors work to promote β cell dysfunction and death through several intersecting mechanisms, including oxidative stress, mitochondrial dysfunction, epigenetic dysregulation and activation of ER stress pathways [18–21,90–92]. In addition, although much less well studied, PPAR-γ activation may also enhance β cell function and survival through activation of non-genomic pathways.

Modulation of ER Stress Pathways

One mechanism through which chronic demand on the β cell to produce and secrete insulin leads to deleterious effects is through the activation of ER stress pathways. Accumulation of mis- or unfolded protein in the ER leads to a state of ER stress and subsequent activation of the unfolded protein response (UPR). The UPR is a multifaceted response aimed at limiting the delivery of new unfolded proteins to the ER. If left unchecked, though, perpetual stimulation of the UPR can lead to activation of apoptotic pathways and β cell death [93]. In recent years, ER stress pathways and their contribution towards progression of pancreatic β cell dysfunction have been the focus of intense investigation (reviewed in [94,95]). In genetic models prone to the development of ER stress, the administration of PPAR-γ agonists has been shown to reduce this process in the β cell. Mice deficient in Wolfram syndrome protein, WFS1, in combination with the agouti mutation develop severe insulin-deficient diabetes by 8 weeks of age. This process is characterized by robust activation of ER stress pathways and loss of β cell mass. Although activation of the UPR persisted in pioglitazone-treated mice, there was a marked protection against the development of diabetes, improvement in ER lumen dilation, with resulting positive effects on β cell mass. The exact mechanisms underlying these benefits, however, were not directly investigated [96].

In db/db mice, the reduction of ER stress with pioglitazone treatment was co-incident with the restoration of Pdx-1 expression, nuclear localization of the histone methyl-transferase Set7/9 and the maintenance of islet euchromatin architecture [68]. In support of these findings, Pdx-1 haploin-sufficient mice have recently been shown to develop diabetes when stressed with high-fat feeding. This phenotype is because of a failed compensatory gain in β cell mass and increased apoptosis, which was attributed to ER stress. Interestingly, in this same report, the *WFS1* gene was also found to be a direct target of Pdx-1 [97]. In aggregate, these findings suggest that the modulation of ER stress by PPAR-γ activation may be closely linked with the maintenance and/or restoration of Pdx-1 levels.

Protection Against Islet Amyloid Polypeptide

Oligomerization of islet amyloid polypeptide into toxic amyloid deposits is also reported to play a prominent role in the progressive β cell dysfunction of type 2 diabetes [98]. Lin and colleagues showed that rosiglitazone was able to prevent IAPP-induced apoptosis in human islets through interference with IAPP toxic oligomer formation. In this report, these effects were mediated through activation of the PI3 kinase pathway and AKT phosphorylation [99]. Whereas supraphysiologic levels of IAPP result in the induction of ER stress pathways [100], a recent report suggests that at levels of IAPP seen in human type 2 diabetes, ER stress is not an obligatory pathway for IAPP-mediated β cell dysfunction [101]. Notwithstanding this controversy, PPAR-γ agonists may also act to modulate IAPP-induced ER stress, although this effect has not been directly characterized.

Reductions in Oxidative Stress

Hyperglycaemia, lipotoxicity and elevated cytokines have all been shown to induce oxidative stress and mitochondrial dysfunction in islets and β cell lines [102,103]. A simple

definition of oxidative stress is any condition that results in the generation of reactive oxygen (ROS) or reactive nitrogen species (RNS) that cannot be dealt with appropriately through normal antioxidant mechanisms [104]. The β cell has limited natural antioxidant capacity and limited capacity for dealing with ROS and RNS, therefore making it a particularly fragile target for oxidative stress [105,106]. In the setting of elevated glucose, glycolytic pathways become saturated and ROS are generated from alternative metabolic pathways, while elevated lipid levels lead to increased lipid esterification and generation of ceramides, which likewise generate oxidative stress [107,108]. Cytokines have also been shown to increase the production of ROS and RNS and lead to impaired islet function. In this regard, Wang and colleagues recently showed that rosiglitazone and pioglitazone were able to block interleukin-1β (IL-1) and interferon-γ (IFN)-induced apoptosis and rescue GSIS in NIT-1 mouse insulinoma cells [109].

Treatment of db/db mice with pioglitazone for 6 weeks improved glucose homeostasis and serum free fatty acid levels as well as islet function and islet insulin content. Pioglitazone treatment reduced islet expression of both hydroxynonenal (HNE) and hemoxygenase 1, which are known to be toxic by-products of oxidative stress [110]. In a similar study, 2 weeks of treatment with pioglitazone was also found to decrease HNE expression in pioglitazone-treated db/db mouse islets. This correlated with an increased expression of the genes encoding several antioxidants including glutathione peroxidase, superoxide dismutase and catalase. Further, pioglitazone treatment decreased the expression of the stress-inducing gene NADPH oxidase [89].

Pioglitazone has been shown to have even shorter term effects to decrease oxidative stress in MIN6 cells treated with high glucose and palmitate. Pharmacological PPAR-γ activation in this system was able to restore partially GSIS and suppress intraislet triglyceride accumulation, while decreasing uncoupling protein-2 (UCP-2) mRNA levels and decreasing the production of reactive oxygen species [111]. UCP-2 is an inner mitochrondrial membrane protein that is induced by ROS and decreases the metabolic efficiency of the β cell by uncoupling oxidative processes from ATP generation. Induction of UCP-2 decreases the ability of the β cell to secrete insulin [112,113]. In aggregate, these results suggest that both short-term and long-term treatments with pioglitazone can decrease islet oxidative stress, which translates into preservation of β cell function and survival in type 2 diabetes.

Protection Against Lipotoxicity

Exposure to elevated serum free fatty acids, ceramides and other toxic lipid intermediates can lead to increased triglyceride accumulation within the islet, which can have profound effects on β cell health [114–117]. The islet-specific KO of the ATP-binding membrane cassette transporter protein A1 (ABCA1) as well as the heterozygous PPAR-γ KO model both show enhanced intraislet triglyceride accumulation and diminished glucose-stimulated insulin secretion [40,118]. ABCA1 is a membrane-associated protein, which plays a key role in intra-cellular cholesterol homeostasis. ABCA1 functions to efflux cellular cholesterol and phospholipids to apolipoproteins and mediates the formation of high-density lipoprotein particles. In the heterozygous PPAR-γ model, treatment with pioglitazone was able to restore GSIS. Rosiglitazone, however, had no effect on glucose intolerance in the ABCA1 KO model, suggesting that the effects of TZDs may be mediated, in part, through ABCA1 [118]. Rosiglitazone has also been found to restore GSIS and decrease apoptosis in isolated human lipotoxic islets. Interestingly, these effects were co-incident with a reduction in intraislet triglyceride accumulation and reduced islet inducible nitric oxide synthase (iNOS) expression [119,120].

Potential Non-genomic Effects of PPAR-γ Agonists

Ligands of PPAR-γ may also function in a receptor- or DNA-independent manner to affect cellular function. These include effects that are too rapid to be explained by changes in gene transcription as well as responses that persist in PPAR-γ null models or following treatment with a PPAR-γ antagonist. Whereas many of the PPAR-γ mediated non-genomic effects have been reviewed in detail elsewhere [121–123], there is limited data on potential non-genomic effects within the pancreatic β cell. Of relevance to the diabetic islet though, PPAR-γ agonists have been shown to suppress inflammatory gene transcription in PPAR-γ null macrophages, suggesting that, in part, the antiinflammatory effects of these agents may occur independent of the receptor [124]. In addition, PPAR-γ has been shown to physically interact with transcriptional co-activators, thereby preventing these factors from binding gene targets leading to repression of inflammatory gene expression [125].

PPAR-γ agonists may also modulate a number of other signalling pathways. For instance, troglitazone has been shown to activate rapidly extracellular signal-regulated kinase (ERK)1/2 in human colorectal cell lines [126]. ERK1/2 signalling has been shown to be important in β cell survival, proliferation and glucose-dependent insulin gene transcription [127–129]. Likewise, the activation of c-Jun N-terminal kinase (JNK) in the islet leads to apoptosis and β cell death. PPAR-γ agonists have been shown to inhibit cytokine-induced activation of JNK in an insulinoma cell line [130]. Further, a recent report examined the metabolic effects of macelignan, a natural compound isolated from Myristica fragrans, which functions as a dual PPAR-γ/α agonist. Treatment of db/db mice with this agent improved glucose homeostasis and reduced JNK activation and ER stress in liver and adipose tissues [131].

The effects of PPAR-γ agonists on insulin signalling in the β cell have also been characterized. Paracrine stimulation of the insulin-signalling pathway in the β cell through phosphoinositide 3 (PI3) kinase and AKT has important implications for glucose homeostasis and β cell survival. Mice with a β cell-specific KO of the insulin receptor show markedly impaired first-phase insulin secretion and progressive glucose intolerance [132]. PPAR-γ agonists have been shown to increase AKT phosphorylation in the setting of both IAPP-and lipid-inducted toxicity. These effects were blocked by PI3 kinase inhibitors and associated with increased levels of insulin receptor substrate 2 (IRS2) protein [133].

Conclusions

There is an abundance of preclinical and human data showing the β cell-specific profunction and prosurvival effects of pharmacological PPAR-γ activation in T2DM. These effects are summarized in figure 1, which illustrates an overall model of PPAR-γ mediated actions in the islet. Pharmacological activation of PPAR-γ has been shown to regulate transcription of several key β cell genes involved in glucose sensing, β cell development, GSIS and insulin gene transcription. Activation of these targets leads to enhanced insulin secretion and gene expression in the diabetic state. Further, treatment with PPAR-γ agonists has a number of prosurvival effects that limit death of the diabetic islet through reductions in cytokine-, lipid-, glucose- and IAPP-induced stress pathways.

Nevertheless, even in the context of this abundance of published data, there are several facets of PPAR-γ biology in the β cell that remain unexplained and require further investigation. First among those is a better understanding of the differences between the genetic models of islet-specific PPAR-γ deletion. More importantly, though, recent clinical data have questioned the safety of TZDs. In particular, use of these agents is associated with osteoporosis, fluid retention and congestive heart failure [134,135]. Even more serious, the use of rosiglitazone has been associated with an increased risk of adverse cardiac outcomes

in diabetic patients [136]. In the clinical setting, these safety concerns should be weighed against the potential benefit of preserving β cell function in T2DM. As a research community, though, these remaining questions should serve as a 'call to action' to embark on studies aimed at explaining the tissue-specific effects of PPAR-γ agonism and understanding the differential molecular effects of specific TZDs. For instance, a recent report used microarray and chromatin immunoprecipitation to characterize regulation of gene expression and chromatin architecture by troglitazone, pioglitazone and rosiglitazone in 3T3-L1 adipocytes. Interestingly, the authors found that these three agents regulated similar but not completely overlapping sets of genes, supporting a model of selective PPAR modulation (SPPARM), analogous to the pharmacologically relevant selective estrogen receptor modulation (SERM) model [137]. These recently described safety concerns in combination with the SPPARM model speak to the importance of continued research into the biology of PPAR-γ . Importantly, these results suggest that ligands for PPAR-γ could and should be created to harness the profunction and prosurvival β cell-specific effects, while minimizing unintended consequences in the cardiovascular system and bone.

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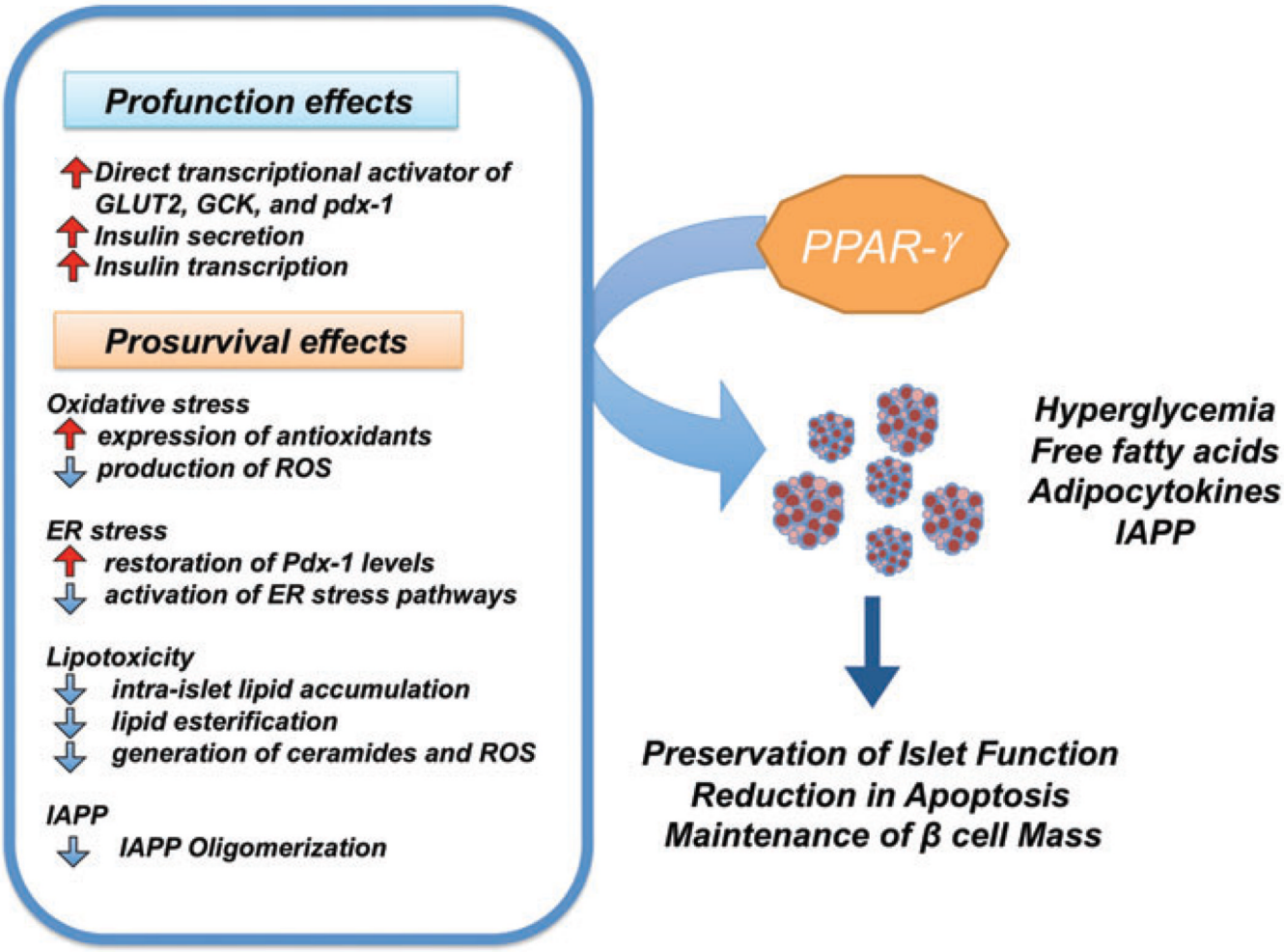

Figure 1.

β cell-specific effects of peroxisome proliferator-activated receptor γ (PPAR-γ) agonists in type 2 diabetes mellitus. PPAR-γ directly regulates key β cell genes involved in glucose sensing, insulin secretion and insulin transcription including pdx-1, GLUT2 and glucokinase. Pharmacological PPAR-γ activation has also been shown to protect against glucose-, lipid-, cytokine- and IAPP-induced activation of stress pathways. These complementary profunction and prosurvival effects of PPAR-γ activation synergize to preserve β cell function and mass in type 2 diabetes mellitus.

Table 1

A summary of human trials which have included direct measurements of β cell function following PPAR-γ agonist treatment in persons with IGT, IFG, T2DM or a history of gestational diabetes.

Study	Patient population	Drug	Length of treatment	Measurements performed	Outcome(s) of improved β cell Function
Cavaghan et al. [38]	IGT	Tro	12 weeks	75 g OGTT IVGTT	Improved insulin secretion rates adjusted for insulin sensitivity
				Graded glucose infusion Spectral analysis for oscillatory glucose infusion	Improved β cell sensing during oscillatory glucose infusion
Prigeon et al. [138]	T2DM	Tro	12 weeks	Acute insulin response to arginine IVGTT	Reduced proinsulin to insulin ratio
Miyazaki et al. [139]	T2DM	Pio	26 weeks	75 g OGTT	Increased plasma insulin response during OGTT
					Increased insulinogenic index (AUC insulin/AUC glucose)
Buchanan et al. (TRIPOD) [31]	History of GDM	Tro	120 weeks	75 g OGTT IVGTT	Troglitazone-treated controls had a stable β cell compensation (DI) for insulin resistance, compared to placebo-treated controls who showed decreasing DI
Juhl et al. [34]	T2DM	Rosi	13 weeks	IVGTT Hyperglycaemic clamp with arginine stimulation	Improved glucose-entrained insulin secretion
				Assessment of baseline high-frequency insulin pulsatility by spectral analysis	
				Hyperinsulinaemic euglycaemic clamp	
Wallace et al. [35]	T2DM	Pio	12 weeks	HOMA IVGTT and hyperglycaemic clamp Euglycaemic hyperinsulinaemic clamp	Increased HOMA-%B Reduced proinsulin to insulin ratio
Xiang et al. (PIPOD) [32]	History of GDM	Pio	36 weeks after TRIPOD study	75 g OGTT IVGTT	Stabilization of AIR_g and DI, compared to placebo-treated controls who had worsening of AIR_g and DI over the same time period
Kahn et al. (ADOPT) [33]	T2DM	Rosi	48 weeks	HOMA	Slower rate of decline in HOMA-%B in rosiglitazone-treated subjects compared to those treated with either glyburide or metformin
Gastaldelli et al. [37]	T2DM	Pio or Rosi	16 weeks	75 g OGTT Two-step euglycaemia insulin clamp	Increased insulin secretion/ insulin resistance index (ISR AUC/glucose AUC + IR)
					Improved insulin secretory response per incremental plasma glucose response expressed in relationship to the severity of insulin resistance (ISR/G_{0-120} + IR)
Hanley et al. (DREAM) [39]	IGT and IFG	Rosi	At least 24 months	75 g OGTT	Increased insulinogenic index which was corrected for HOMA-IR
					Decreased fasting proinsulin-to-C-peptide ratio

ADOPT, A Diabetes Outcome Progression Trial; AIR_g, acute insulin secretion during IVGTT; AUC, area under the curve; DI, disposition index; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; GDM, gestational diabetes mellitus; HOMA, homeostasis model of assessment; HOMA-IR, homeostasis model of assessment of insulin resistance; HOMA-%B, homeostasis model of assessment of β cell function; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISR, insulin secretory response; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; pio, pioglitazone; rosi, rosiglitazone; T2DM, type 2 diabetes mellitus; TRIPOD, TRoglitazone In the Prevention Of Diabetes; tro, troglitazone.