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Peroxisome proliferator-activated receptors and renal diseases

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1. ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. Three isoforms of PPAR, i.e., PPAR-α, -δ, and -γ, have been identified and are differentially expressed in various tissues, including the kidney. The target genes of PPARs are involved in diverse biological processes, including adipogenesis, lipid metabolism, insulin sensitivity, inflammatory response, reproduction, and cell growth and differentiation. PPARs have been reported to protect against renal injury through indirect systemic effects and/or direct renal effects in diabetic nephropathy, glomerulonephritis, renal cell carcinoma, acute renal failure and chronic renal disease. In this review, we summarize the role of the three identified PPAR isoforms, PPARα, -δ, and -γ, in renal physiology and discuss the renoprotective effects of PPAR ligands in various kidney diseases.

2. INTRODUCTION

The kidney plays a key role in regulating sodium and water homeostasis and blood pressure. Loss of renal function therefore causes many systemic disorders, including cardiovascular diseases and hypertension. With the prevalence of type 2 diabetes, diabetic renal complications, or diabetic nephropathy -- one of the major complications of diabetes -- has become a worldwide serious public-health concern, although glomerulonephritis, renal cell carcinoma and acute renal failure remain common renal diseases. If left untreated, these diseases progress to chronic kidney disease and, ultimately, end–stage renal disease (ESRD) (1). With ESRD, kidneys fail to function, which results in sodium and water retention and accumulation of metabolic wastes and many toxic substances. Renal system data from 2004 in the United States revealed kidney disease as a major health problem; approximately 20 million patients had the disease.

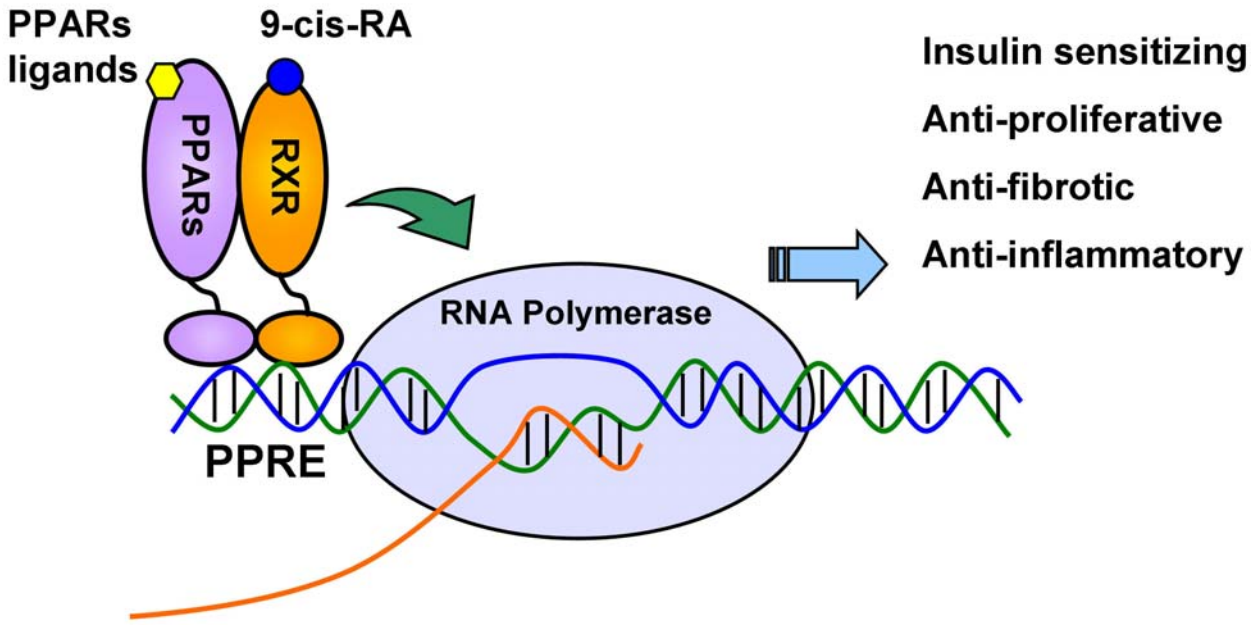

Figure 1. Schematic representation of the mode of action of PPARs. The PPAR isoforms form heterodimers with retinoid X receptor α (RXRα) in the presence of their ligands. The resulting heterodimer binds to PPAR response elements (PPRE) in the promoter regions of PPAR-driven genes, which are involved in many biological processes closely related to renoprotective effects, including insulin sensitizing, and anti-proliferative, anti-fibrotic, and anti-inflammatory actions.

Therefore, effective treatment of renal diseases is urgently needed.

As a subfamily of metabolic nuclear receptors, peroxisome proliferator-activated receptors (PPARs) participate in various biological processes, including lipid metabolism, adipogenesis, immune response, insulin sensitivity, reproduction and cell growth and differentiation (2). With the remarkable clinical effects of PPAR synthetic ligands, the role of PPARs in renal disease has received a lot of attention. In this review, we summarize the role of the three identified PPAR isoforms, PPARα, -δ, and -γ, (3) in renal physiology and discuss the renoprotective effects of PPAR ligands in various kidney diseases.

3. PPARS: LIGANDS AND BIOLOGICAL ROLES

PPARs are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. The three isoforms of PPAR, products of distinct genes, constitute the NR1C group in the nomenclature of nuclear receptors (4). In the presence of their specific ligands, PPARs usually heterodimerize with another nuclear receptor, retinoid X receptor α, forming a transcriptional complex that binds to a specific DNA sequence, peroxisome proliferator-response element, within the promoter regions of PPAR target genes. These genes are involved in diverse biological processes (Figure 1).

PPARα, the first member of the PPAR subfamily identified, is highly abundant in tissues with high fatty acid oxidation activity, including the liver, kidney, intestine mucosa, heart and brown adipose (5, 6). Endogenous ligands such as polyunsaturated fatty acids and synthetic ligands, including lipid-lowering fibrates (e.g., fenofibrate, clofibrate), can effectively activate PPARα and regulate the transcription of an array of genes involved in lipid metabolism and inflammatory response (7, 8) (Table 1).

PPARδ seems to be ubiquitously expressed at low levels in almost all tissues examined (6). The endogenous arachidonic-acid cyclooxygenase metabolite prostacyclin and synthetic compounds including L-165041 and GW2433 have been shown to selectively activate PPARδ. A large body of evidence suggests that PPARδ is involved in fatty acid and lipid metabolism and may be a pivotal factor in metabolic control (9). Recently, PPARδ has also been reported to be important in maintaining renal cell survival in hyperosmotic medulla (10).

PPARγ is expressed predominantly in adipose tissue, with low levels in stomach, intestine, urinary bladder, kidney, spleen, adrenal, liver, lung, brain, heart and vasculature (5, 6). PPARγ controls adipocyte proliferation and differentiation and therefore plays an important role in regulation of lipid storage and insulin sensitivity (11). PPARγ can be bound and activated by various small lipophilic compounds, including naturally occurring 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) and EETs and synthetic antidiabetic thiazolidinediones (TZDs) (e.g., rosiglitazone, pioglitazone), which are beneficial for improving insulin sensitivity. The main biological functions, ligands and distribution of expression of PPARs are summarized in Table 1.

Table 1. Biological roles, ligands and tissue distribution of PPAR isoforms.

Name	Biological functions	Ligands	Expression	Reference
PPARα[1]	β-oxidation, fatty acid transport, lipoprotein synthesis, inflammatory response	8-S-hydroxyeicosatetraenoic acid, leukotriene B4, synthetic fibrates	Abundant in liver, kidney, heart, brown adipose	8
PPARδ	Lipid metabolism	PGI2[2], synthetic compounds L-165041, GW2433	Ubiquitously expressed in almost all tissues	9
PPARγ	Adipocyte proliferation and differentiation, lipid storage, insulin sensitivity	15d-PGJ2[3], synthetic TZDs[4]	Predominantly expressed in adipose tissue, also mildly expressed in other tissues	11

Abbreviations: PPARα[1], Peroxisome proliferator-activated receptor α; PGI2[2], prostaglandin I2; 15d-PGJ2[3], 15-deoxy-Δ12,14-prostaglandin J2; TZDs[4], thiazolidinediones.

4. PPAR ligands: Clinical implications and side effects

Currently, the synthetic PPARα ligand fenofibrate (Lipanthyl/Tricor), and PPARγ ligands rosiglitazone (Avandia) and pioglitazone (Actos) have been used in clinical practice as lipid-lowering therapy and oral antidiabetic drugs, respectively. However, the use of these ligands may result in many side effects, including increased serum creatinine level (12), fluid retention and increased cardiovascular risk (13, 14). Recent research interest has focused on developing novel compounds possessing both PPARα- and PPARγ-activating properties to benefit both plasma glucose control and lipid levels. To date, many PPARα/γ dual agonists have been developed and have shown promising therapeutic effects. However, the first generation of PPARα/γ dual agonists, tesaglitazar (Galida) and muraglitazar (Pargluva), were withdrawn from phase III clinical trials because of their poor safety profile. The next generation of fine-tuned dual PPARα/γ agonists prefers agonists with full PPARα and partial PPARγ activity.

5. PPARS: INTRARENAL LOCALIZATION

All three PPAR isoforms are functionally expressed in the kidney. PPARα is highly expressed in the epithelial cells of proximal tubules and medullary thick ascending limbs, with much lower levels in glomerular mesangial cells (15-17), whereas PPARγ is expressed primarily in the epithelium of distal medullary collecting ducts and to a lesser extent in the glomerular mesangial cells, endothelial cells and podocytes, proximal tubular cells, endothelial cells of renal microvasculature, and interstitial fibroblast cells (15, 18). In the kidney, PPARδ seems to be diffusely expressed in the renal cortex and medulla, with relatively higher levels in medullary interstitial and stromal cells (15). The differential intrarenal localization of all three PPAR isoforms suggests that they play distinct roles in maintaining normal renal functions. In the following sections, we discuss the role of the three PPAR isoforms in renal pathophysiological settings and the therapeutic potential of PPAR ligands in various renal diseases, especially diabetic nephropathy.

6. PPARs: therapeutic role in renal diseases

6.1. PPARα and renal disease

As mentioned above, in the kidney, PPARα is selectively expressed in the proximal tubule cells, where its activation is essential for renal fatty acid metabolism, energy homeostasis, and anti-inflammatory regulation (3, 18). Large numbers of studies have indicated that PPARα agonists significantly attenuate renal injury in various kidney diseases such as diabetic nephropathy, acute renal failure, glomerulonephritis, and chronic renal failure (19-22). Thus, PPARα could serve as an important renoprotective factor contributing to the prevention or delay of renal disease progression.

6.1.1. PPARα and diabetic nephropathy

Increasing evidence suggests that PPARα activators are effective in improving insulin resistance in type 2 diabetic patients with the insulin resistance syndrome (23). Indeed, Park *et al.* showed that fenofibrate treatment reduced fasting blood glucose, ameliorated insulin resistance, reduced hypertrophy of pancreatic islets, and reduced urinary albumin excretion in diabetic animals (19). To date, multiple mechanisms have been proposed for the hypoglycemic and insulin-sensitizing effect of PPARα agonists. Fibrates have been reported to reduce the triglyceride content in skeletal muscle (24, 25), which is associated with improved insulin sensitivity (26). PPARα agonists have also been found to increase hepatic fatty acid catabolism, thus resulting in decreased systemic and tissue free fatty acid content (27). Koh *et al.* showed that fenofibrate treatment prevented the development of diabetes in Otsuka Long Evans Tokushima Fatty (OLETF) rats by reducing adiposity, improving peripheral insulin sensitivity, and exerting beneficial effects on pancreatic β-cells (24). Recently, Mishra *et al.* demonstrated that PPARα is a diabetes-induced transcription factor that helps control the renal response to lipids (28). Moreover, the renal-protective effects of fenofibrate might be achieved through the reduction of glomerular hypertrophy and mesangial matrix accumulation (19, 29). Taken together, these data suggest that PPARα may represent a potential therapeutic target for treating insulin resistance and type 2 diabetes and preventing diabetic renal complications.

Interestingly, several recent studies have found a paradoxical phenomenon, that PPARα deletion has a protective effect similar to that of its ligands in mice with insulin resistance induced by high-fat diet. Insulin resistance was improved in both young and old PPARα-null mice (30-32). As expected, the old PPARα-null mice showed milder albuminuria than wild-type mice (32). To date, the underlying mechanisms remain unknown and require further investigation.

6.1.2. PPARα and acute renal failure

Recently, Portilla *et al.* revealed that PPARα plays an important protective role in acute renal tubular injury induced by ischemia/reperfusion and cisplatin. Cisplatin is one of the most common antitumor agents used

in chemotherapy for malignant disease, and its major side effect is nephrotoxicity. Synthetic PPARα ligands attenuate cisplatin-induced acute renal injury by preventing the inhibition of fatty acid oxidation (33), reducing apoptosis and necrosis of the proximal tubules through decreasing endonuclease G activity (34), and limiting inflammatory processes by blocking NF-κB activity (21, 35). Most recently, Kamijo *et al.* demonstrated that injection of fatty acid-binding albumin into PPARα-null mice resulted in more severe tubular lesions than in wild-type mice, which provides further evidence that PPARα is a renoprotective factor (36). Similarily, the PPARα agonist was shown to protect against ischemic renal injury via preservation of renal acyl CoA oxidase and cytochrome P450 4A1 gene expression through a PPARα-dependent pathway during ischemia/reperfusion injury (37). The renal protective action of the PPARα agonist in ischemia and nephrotoxin-induced renal tubular injury appears to be PPARα dependent, since PPARα gene-deficient mice subjected to renal ischemia/reperfusion or treated with nephrotoxins exhibited enhanced cortical necrosis and impaired renal function (37, 38).

6.1.3. PPARα and glomerulonephritis

In recent years, the immunoregulatory activity of ligands for PPARs has attracted intensive attention (39, 40). Anti-glomerular basement membrane (GBM) glomerulonephritis characterized by crescent formation and necrotizing inflammation of glomerular capillaries is the most severe form of glomerulonephritis. By using a rat anti-GBM glomerulonephritis model, Saga *et al.* found that bezafibrate, a PPARα agonist, can markedly suppress anti-GBM crescentic glomerulonephritis (41). In accordance with this result, Kamijo *et al.* recently reported that PPARα can protect against glomerulonephritis induced by long-term exposure to the plasticizer di- (2-ethylhexyl)phthalate (42). All these findings suggest that PPARα might be a novel therapeutic target for the treatment of glomerulonephritis.

6.2. PPARδ and renal disease

PPARδ plays a key role in biological processes such as fertility, lipid metabolism, bone formation, mast cell immunity, skin and brain development, wound healing, and tumorigenesis. Although PPARδ mRNA is detected in almost all tissues and cells examined, it is relatively abundant in the kidney, with ubiquitous expression in all nephron segments (15).

Because of the high expression level in the kidney, PPARδ participates in renal physiological regulation and pathophysiological processes. Letavernier *et al.* provided evidence that PPARδ may protect the kidney against ischemia/reperfusion-induced acute renal failure by activating the antiapoptotic Akt signaling pathway and increasing the spread of tubular epithelial cells. In this study, PPARδ+/- and PPARδ-/- mutant mice showed more severe kidney dysfunction and injury than wild-type mice. Wild-type mice pre-treated with the PPARδ agonist were completely protected against renal dysfunction (43).

Moreover, although nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common pain relief medicines in the world, they are well recognized as a major class of therapeutic agent that causes renal papillary necrosis (44). Inhibition of PPARδ activity may contribute to this side effect (10). Overexpression of PPARδ can prevent medullary interstitial cell death due to reduced ability to tolerate hypertonic stress by COX2 inhibition, which suggests that PPARδ might be an important survival factor for medullary interstitial cells in the hypertonic condition in the renal medulla.

PPARδ may also be involved in the pathogenesis of diabetic nephropathy. Overexpression or activation of PPARδ in skeletal muscle can significantly improve mouse endurance exercise ability, and resist to obesity with improved metabolic profiles, even in the absence of exercise (45). Regarding the direct renal effects, Escher *et al.* have recently found the PPARδ mRNA level in the kidney remarkably down-regulated after an overnight fast and quickly restored to the normal level upon refeeding (46). In addition to nutritional regulation, the expression of PPARδ in the kidney was also down-regulated in type 1 diabetic Akita and OVE26 mice, which resulted in decreased fatty acid oxidation and increased renal triglyceride accumulation (47). These findings provide strong evidence that PPARδ activation may be beneficial for amelioration of diabetic nephropathy.

6.3. PPARγ and renal disease

Although TZDs are a group of insulin sensitizers and are widely used in clinical therapy for type 2 diabetes, their renoprotective actions are just now being carefully evaluated. Increasing evidence has revealed the protective effects of PPARγ activation on diabetic nephropathy, renal cell carcinoma, renal failure and glomerulonephritis, which strongly suggests that PPARγ may be a potential therapeutic target for the treatment of these renal diseases (48-51). The mechanisms mediating the renoprotective effect of PPARγ ligands may involve both systemic metabolic control and direct action on the kidney.

6.3.1. PPARγ and diabetic nephropathy

As one of the major complications of diabetes, diabetic nephropathy is characterized by renal hypertrophy and extracellular matrix accumulation, which without effective intervention eventually progresses to fibrosis with loss of renal function. PPARγ agonist TZDs may hold great promise for treating both insulin resistance and diabetic renal complications. The therapeutic effects of TZDs on prevention or even reversal of the progression of diabetic nephropathy are achieved possibly through both indirect systemic and direct renal effects (Figure 2).

PPARγ exerts its insulin-sensitizing effects in adipose tissue, skeletal muscle, liver, and pancreatic β-cells. Loss-of-function mutation of PPARγ results in severe insulin resistance, partial lipodystrophy, diabetes, hypertension and dyslipidemia in humans, in part because of excessive lipid accumulation in skeletal muscle and liver (52). PPARγ-agonist TZDs increase the sensitivity of the liver to insulin-stimulated suppression of gluconeogenesis and enhance glucose utilization in the skeletal muscle (53). In the adipose tissue, PPARγ activation increases glucose uptake and results in profound changes in adipokine

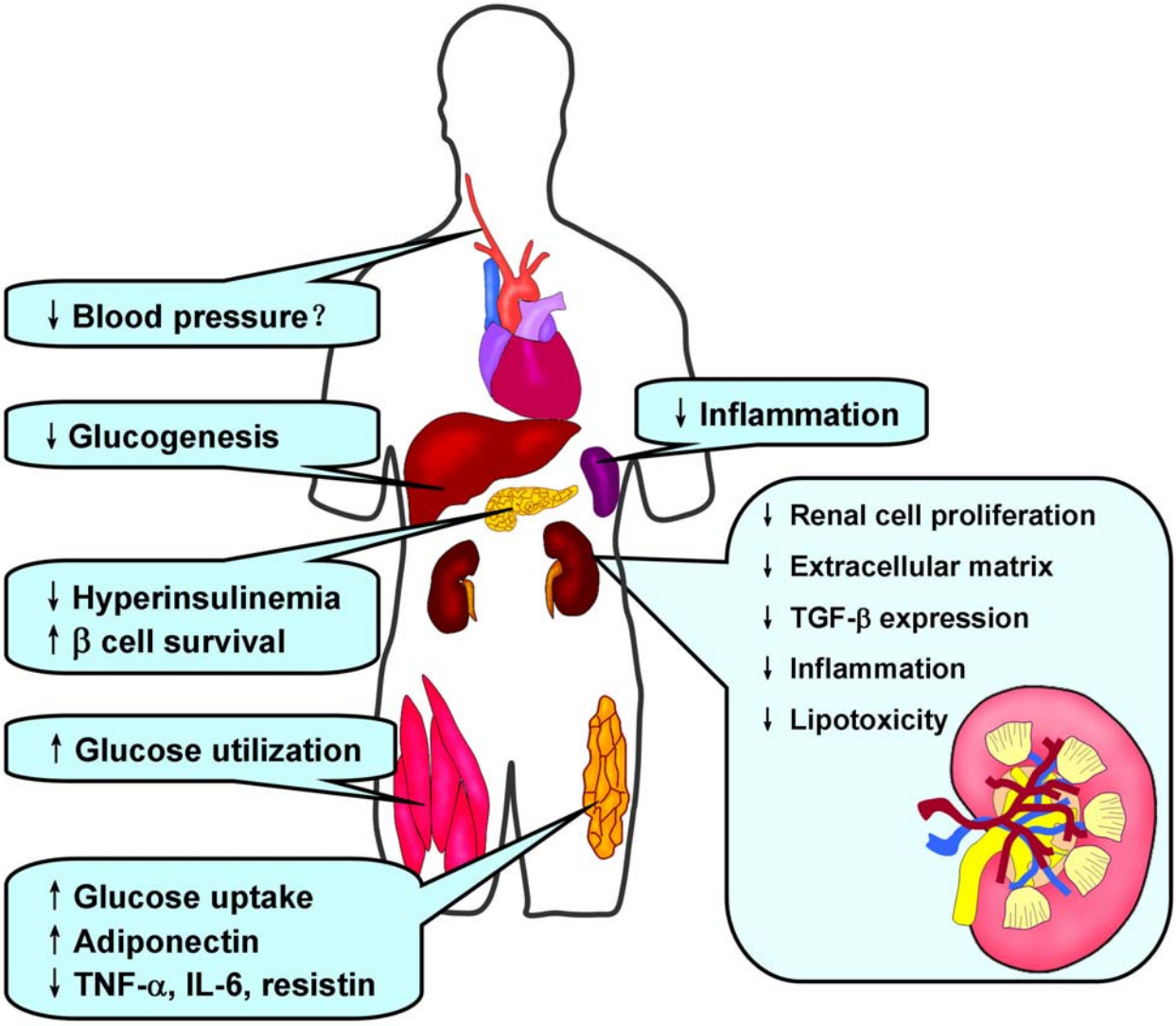

Figure 2. Summary of the therapeutic actions of PPARγ in diabetic nephropathy**.** Both systemic action and direct renal effect are involved in the renoprotective effect of PPARγ agonists. TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β; IL-6, interleukin 6.

expression and secretion, including suppression of insulin-desensitizing tumor necrosis factor α (TNF-α)**,** interleukin-6 (IL-6) and resistin, and induction of insulin-sensitizing adiponectin and visfatin (54-58). In a recent study, activation of PPARγ protected pancreatic β-cells from cytokine-induced cytotoxicity (59). In addition, PPARγ can act as an anti-inflammatory factor to reduce the production of cytokines (TNF-α, IL-1, and IL-6) (60), probably by inhibiting the activity of pro-inflammatory transcription factors such as nuclear factor κB (NF-κB), activator protein 1 (AP-1) and signal transducer and activator of transcription (STAT) (61). The anti-inflammatory effect of PPARγ is highly beneficial, since low-grade inflammation is associated with the pathogenesis of insulin resistance (62). Thus, systemic effects such as improving insulin resistance and attenuating inflammation may represent two major mechanisms mediating the beneficial effect of PPARγ on glycemic control in type 2 diabetes, thereby preventing the development or slowing the progression of diabetic nephropathy. PPARγ may also benefit the kidney by lowering blood pressure. Although results remain inconclusive (63, 64), PPARγ activation is believed to be effective in lowering blood pressure via attenuating the activity of the renin-angiotensin system and mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase, and ROS-generating enzymes (65-67). Interestingly, several lines of evidence point to an insulin-sensitizing action of PPARγ antagonism (68-70). Although the underlying mechanism is unknown, these observations suggest that the PPARγ antagonist may also have potential therapeutic implication in insulin resistance and type 2 diabetes.

Abundant evidence from studies of patients, animal models, and cell models has shown that local activation of PPARγ in the kidney is involved in its

renoprotection. TZD therapy was repeatedly reported to be effective in reducing microalbuminuria in patients with type 2 diabetes (71-73). Compared to other oral hypoglycemic agents (including insulin, metformin, glyburide, and glibenclamide), all TZD PPARγ agonists (troglitazone, rosiglitazone, and pioglitazone) produce similar glycemic control but appear to provide superior renal protection in patients with type 2 diabetes (74-76). For example, Miyazaki *et al.* recently reported that 12 weeks of rosiglitazone treatment significantly decreased albuminuria, which might be due at least in part to direct activation of renal PPARγ (48). Consistent with these clinical observations, PPARγ-agonist TZDs have been shown to improve diabetic nephropathy in animal models of both type 1 and type 2 diabetes (75, 77-80). Indeed, troglitazone treatment significantly decreased albuminuria, reduced glomerular hyperfiltration, ameliorated mesangial expansion, and inhibited renal matrix protein and TGF-β expression in the kidney of streptozotocin-induced type 1 and Zucker type 2 diabetic rats (79, 81, 82). As well, Baylis *et al.* (80) demonstrated that rosiglitazone treatment reduced albuminuria, improved glomerular filtration rate, and normalized glomerulosclerosis and tubulointerstitial fibrosis in obese type 2 diabetic rats. Importantly, a recent report showed that telmisartan is a weak PPARγ agonist and its treatment slows the progression of diabetic nephropathy (83). This observation suggests that the renoprotective effect of angiotensin II type 1 receptor blockers may be attributed to PPARγ activation in part.

Studies of cultured renal cells provide strong support for the possibility that direct renal action may also be involved in mediating the beneficial renal effect of PPARγ agonists. PPARγ agonists can inhibit the proinflammatory phenotype induced by advanced glycosylation end products (AGE) in cultured renal proximal tubular epithelial cells through STAT-1–mediated pathways involving IL-8 and intercellular adhesion molecule 1 (ICAM-1) (84). PPARγ activators are also reported to significantly suppress the expression of transforming growth factor β (TGF-β), type IV collagen and ICAM-1 and infiltration of macrophages in the kidneys of diabetic rats, as well as inhibit NF-κB and ICAM-1 in cultured glomerular endothelial cells and mesangial cells (82, 85, 86). In addition, PPARγ ligand treatment inhibits cell growth and promotes cell differentiation in cultured mesangial cells (18, 87). Activation of PPARγ markedly blocked AGE-induced MAPK activity (88) and high glucose-stimulated vascular endothelial-cell growth factor expression (89), which is consistent with the inhibitory effect of PPARγ on cell proliferation of mesangial cells. Furthermore, TZDs ameliorate diabetic nephropathy via cell cycle-dependent mechanisms by inhibiting activity of p44/42 MAPK and bcl-2-dependent p27 (90). In the proximal tubular HK2 cells, activation of PPARγ induces the G1-phase cell-cycle arrest and suppresses high glucose-induced AP-1 activity and monocyte chemoattractant protein 1 expression (91). Collectively, these studies suggest that PPARγ has anti-inflammatory and antiproliferative effects in various renal cells, thereby attenuating diabetic renal complications.

In addition, increasing evidence supports the idea that antifibrotic effect of TZDs may also represent an important mechanism by which PPARγ agonists improve diabetic nephropathy (Table 2). TZDs can ameliorate renal fibrosis by regulating many fibrosis relevant genes. Treatment of human cortical fibroblasts with pioglitazone exhibited an antiproliferative and hypertrophic effect with reduced type IV collagen and fibronectin secretion, suppressed matrix metalloproteinase-9 (MMP-9) activity, and decreased tissue inhibitor of metalloproteinase-1 (TIMP-1) and TIMP-2 production (92). Similar result was observed in human proximal tubular cells. PPARγ agonists exerted antifibrotic actions by attenuating the increase in AP-1, TGF-β1, and the extracellular matrix protein fibronectin (93). Antifibrotic hepatocyte growth factor (HGF) was found to be a direct target gene of PPARγ in mesangial cells and renal interstitial fibroblasts (94). In addition, PPARγ agonists activated c-met receptor tyrosine phosphorylation, induced Smad transcriptional co-repressor TG-interacting factor (TGIF) expression, and blocked TGF-β/Smad-mediated gene transcription in mesangial cells. Ablation of c-met receptor through the LoxP-Cre system in mesangial cells abolished the antifibrotic effect of 15d-PGJ2 (94). These antifibrotic effects of PPARγ agonists in multiple cultured renal cells were consistent with the *in vivo* findings that PPARγ activation improved diabetic nephropathy not only in type 1 (95), but also in type 2 diabetes (96).

Taken together, PPARγ agonists can improve albuminuria and slow the progression of glomerulosclerosis in patients with type 2 diabetes and in animal models. Because of these desirable renoprotective effects, PPARγ is a promising target for treating glomerular fibrotic diseases, especially diabetic nephropathy.

It is worth mentioning that combined treatment with PPARα and PPARγ agonists may have better therapeutic potential than each alone in the treatment of type 2 diabetes and diabetic nephropathy. Increasing evidence from both clinical trials and animal experiments show that PPARα/γ dual agonists have striking effects on improvement of insulin resistance, hyperglycemia, dyslipidemia, blood pressure and β-cell function in type 2 diabetes (92, 97-106). In addition, the renoprotective effect of the dual agonists has been recently evaluated and shown marked reduction in albuminuria and renal glomerular fibrosis in both type 1 and type 2 diabetic mice (95, 96).

6.3.2. PPARγ and renal cell carcinoma

Research into the impact of PPARγ on renal cell carcinoma was initiated in 2001. Inoue *et al.* found that PPARγ has strong immunoreactive expression in renal cancer tissues and the PPARγ agonists inhibit the growth of renal cancer cell lines (107). The underlying mechanism might be that TZDs inhibit cell proliferation and induce apoptosis by down-regulating the expression of cyclin D1, Cdk4, vascular endothelial growth factor and basic fibroblast growth factor while up-regulating the expression of p21 and p27 (49, 108, 109). However, the *in vivo* efficacy of PPARγ agonist in animal models has not been tested, and such studies would address the important

Table 2. Genes involved in antifibrotic action of TZDs in renal cells

Cell type	Genes relevant to fibrosis		Reference
Cortical fibroblast	↓type IV collagen ↓fibronectin	↓MMP-9[1] ↓TIMP-1[2] ↓TIMP-2	92
Proximal tubular cell	↓AP-1[3] ↓TGF-β1[4]	↓fibronectin	93
Mesangial cell, Interstitial fibroblast	↑HGF[5] ↑TGIF[6] ↓TGF-β1 ↓PAI-1[7]	↓α-SMA[8] ↓fibronectin ↓Smad	94

Abbreviations: MMP-9[1], matrix metalloproteinase-9; TIMP-1[2], tissue inhibitor of metalloproteinase-1; AP-1[3], activator protein 1; TGF-β1[4], transforming growth factor β1; HGF[5], hepatocyte growth factor; TGIF[6], TG-interacting factor; PAI-1[7], plasminogen activator inhibitor-1; α-SMA[8], α-smooth muscle actin.

question of whether PPARγ could be a therapeutic target for the treatment of renal tumors.

It should be noticed that although agonists of PPARα and PPARγ are generally believed to be antitumor agents, little is know about the potential safety issues that could be involved in the use of PPARδ agonist. Unlike PPARα and PPARγ, activation of PPARδ has been reported to be associated with accelerate intestinal adenoma growth (110), suggesting PPARδ may be carcinogenic.

6.3.3. PPARγ and other kidney diseases

PPARγ activation also has a protective effect on nephritis. In a nephrotoxic serum-induced nephritic rat model, PPARγ agonists markedly alleviated crescentic glomerulonephritis by inhibiting the infiltration of ED-1-positive monocyte/macrophages and CD8-positive cells into glomeruli (111). A similar protection was observed in a nondiabetic glomerulosclerotic rat model made by 5/6 nephrectomy. In this study, troglitazone treatment reduced albuminuria, serum creatinine level, and glomerulosclerosis through decreasing glomerular cell proliferation, in parallel with decreased mRNA expression of p21 and p27 (50). The renoprotective effect of PPARγ agonists on renal cell carcinoma and glomerular fibrosis seems to share a similar pathway involving cell cycle arrest, thereby inhibiting cell proliferation.

Interestingly, endotoxin (lipopolysaccharide, LPS) can protect the kidney against ischemia/reperfusion-induced renal injury by inducing endogenous ligands of PPARγ such as lysophosphatidic acid and 15d-PGJ2, which could be abolished by the selective PPARγ antagonist GW9662 (112). The PPARγ endogenous ligand 15d-PGJ2 can protect renal function in acute renal failure caused by ischemia/reperfusion (113) or in multiple organ failure caused by endotoxin (114). As well, pretreating rats with TZD decreased cell apoptosis in injured kidney induced by ischemia-reperfusion by inducing hepatocyte growth factor (51). In addition, PPARγ mRNA and protein levels were reduced in rats with glycerol-induced acute renal failure. When PPARγ expression was restored by the PPARγ inducer ciglitazone, the renal dysfunction was markedly ameliorated (115, 116).

Finally, it should be mentioned that TZD treatment can cause severe side effects, such as weight gain, fluid retention, and increased cardiovascular risk (13, 14, 48). Fluid retention has been found to be caused by the up-regulation of one PPARγ target gene, epithelial Na^+ channel which is located in the collecting duct and mediates Na^+ reabsorption. The collecting duct-specific diuretic amiloride can block this pathway and might provide one potential specific therapy (13, 117). In addition, extrarenal mechanisms are also involved in TZD-induced fluid retention. As discussed above, PPARγ can lower blood pressure, which may contribute to reduced water excretion (118). The vasodepressor action of TZD demonstrated by using human arterial resistance vessels could cause fluid retention as well (119). Moreover, the altered endothelial permeability, interstitial ion transport, and sympathetic nervous system activity have been reported to be associated with the development of edema following TZD treatment (120).

7. CONCLUSION

PPARs are transcription factors and nuclear receptors. They are widely expressed throughout the body and differentially located in the kidney. Activation of the three PPAR isoforms can result in distinct but overlapping biological processes. Through both indirect systemic effects and direct renal actions, agonists of PPARs hold great promise for treatment of diabetic nephropathy, glomerulonephritis, acute renal failure and chronic renal disease. PPARγ could also represent a therapeutic target for renal cell carcinoma. However, before considering a translational approach, the benefits/risks of using PPAR agonists should be carefully evaluated. Increasing reports suggest that PPARα and PPARγ agonists may cause severe undesirable effects. Thus, caution should be taken in use of these agonists in clinical therapy for diabetes and renal diseases.

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