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*Full Review*

# Peroxisome proliferator activating receptor-γ and the podocyte

Caroline Platt and Richard J. Coward

Academic Children Renal Unit, School of Clinical Sciences, Dorothy Hodgkin Building, University of Bristol, Bristol, UK

Correspondence and offprint requests to: Richard Coward; E-mail: richard.coward@bristol.ac.uk

## ABSTRACT

Over the past two decades it has become clear that the glomerular podocyte is a key cell in preventing albuminuria, kidney failure and cardiovascular morbidity. Understanding the key pathways that protect the podocyte in times of glomerular stress, which can also be therapeutically manipulated, are highly attractive. In the following review we assess the evidence that the peroxisome proliferator activating receptor (PPAR) agonists are beneficial for podocyte and kidney function with a focus on PPAR-γ. We explain our current understanding of the mechanisms of action of these agonists and the evidence they are beneficial in diabetic and non-diabetic kidney disease. We also outline why these drugs have not been widely used for kidney disease in the past but they may be in the future.

**Keywords:** kidney disease, podocyte, PPAR-γ, PPAR-α, thiazolidinediones

## INTRODUCTION

Podocytes are highly specialized, terminally differentiated cells that form a major constituent of the kidney's glomerular filtration barrier (GFB). Their interdigitating foot processes and slit diaphragm are two key components that allow for this specialized functioning. Damage to the podocyte is a common pathological event in many glomerular diseases [1]. Research efforts have focused on finding protective pathways in this cell to exploit, and therapeutic agents such as the peroxisome proliferator activating receptor (PPAR) agonists have shown great promise. We will describe the molecular mechanisms of the thiazolidinedione (TZD)–PPAR interaction, with particular focus on PPAR-γ (the best characterized isoform within this group of nuclear hormone receptors). Through this we will explain why manipulation of these pathways may enhance podocyte and kidney health and be therapeutically attractive.

## THE PPARs

The PPARs are a group of nuclear hormone receptors and ligand-activated transcription factors. They work through heterodimerization with the retinoid x receptor (RXR) to activate gene cassettes involved in a wide variety of tissue-specific cellular processes [2, 3] (Table 1). Ligands (synthetic and endogenous) bind to a specific domain within the PPAR (this is the case for all subtypes) and facilitate a conformational change that allows the recruitment of cofactors that, in turn modulate PPAR activity and effect gene transcription (Figure 1) [12].

The first PPAR to be cloned (from rat hepatocytes) was PPAR-α. Three further subtypes (β, δ and γ) of the receptor were subsequently cloned from frog (*Xenopus*) cDNA [13]. They each have different tissue expression profiles within the body, however, the kidney expresses all four [14] (Table 1). All PPARs have been detected in rodent and human podocytes [15].

Specific mutations in each of the PPARs have been detected that cause a variety of human phenotypes as illustrated in Table 2.

## PPAR-γ

The PPAR-γ gene is located on chromosome 3 in humans (locus 3p25.2) and extends over 100 kb with nine exons that give rise to three transcripts (γ1, γ2 and γ3). Alternate transcription start sites and splicing generates the three transcripts [4]. Six exons are common to all three transcripts. The γ1 and γ3 transcripts give rise to the same protein because their additional exons located at the 5′ terminal (A1 and A2 for γ1 and A2 for γ3) remain untranslated. γ3 mRNA expression is limited to white adipose tissue in humans and its functional significance is uncertain.

The PPAR-γ protein, located in the cellular nucleus, contains 505 amino acids and has a molecular weight of 57.6 kDa. There

**Table 1. The PPARs at tissue and cellular level [3–8]**

| Isoform | Expression profile | Chromosomal location | Synthetics ligands | Natural ligands | Renal distribution |
|---|---|---|---|---|---|
| PPAR-α | Adipose<br>Liver<br>Heart<br>Muscle<br>Renal cortex<br>Lung<br>Placenta<br>Intestine<br>Pancreas<br>Skeletal muscle | C22 (human)<br><br>C15 (mouse) | Fibrates: clofibrate, benzafibrate<br><br>TZDs: KRP-297<br><br>NSAIDs (partial agonists): ibuprofen, indomethacin<br><br><br>Phenylacetic acid derivatives (potent agonists) | Fatty acids<br><br>Eicosanoid derivatives | Proximal tubules<br><br>Medullary thick ascending limb<br><br>Podocytes (mouse and human) |
| PPAR-β/δ | Ubiquitous | C6 (human)<br>C17 (mouse) | GW-501516<br>Phenylacetic acid derivatives (potent agonist) | Fatty acids<br>Eicosanoid derivatives | Ubiquitous |
| PPAR-γ | Adipose[a]<br>Renal medulla<br>Bladder<br>Skeletal muscle<br>Liver<br>Heart<br>Macrophages<br>Vascular smooth muscle<br>Malignant epithelial cells<br>Endothelium<br>Bone marrow | C3 (human)<br><br>C6 (mouse) | TZDs<br><br>–Rosiglitzone[b]<br>– Ciglitazone<br>– Troglitazone<br>– Englitazone<br><br>NSAIDs (partial agonist):<br>– Ibuprofen<br>– Indomethacin<br>Phenylacetic acid derivatives (potent agonist)<br>GW2570 (potent)[c] | Fatty acids<br><br>Eicosanoid derivatives<br>PUFAs in particular:<br>– Arachidonic acid<br>– Linoleic acid<br>– Linolenic acid<br>Xenobiotics | Glomeruli<br>Medullary collecting duct<br>Pelvic urothelium<br>Mesangial cells<br>Podocytes (mouse and human) |

[a]Adipose is the predominant site of PPAR-γ expression and Rosiglitazone has high affinity for the PPAR-γ receptor.
[b]Binding with high affinity, the rest do not bind so strongly.
[c]PPAR-γ agonist with anti-diabetic activity in humans

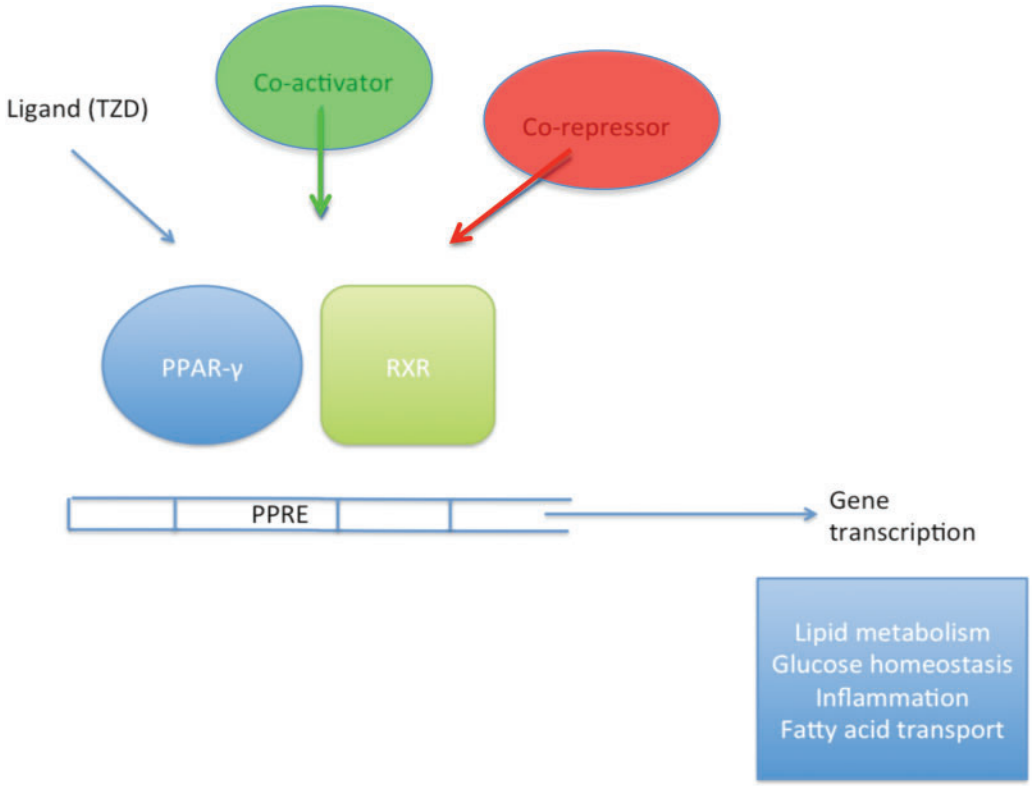


**FIGURE 1:** Inside the nucleus, a simplified illustration of the mechanism through which PPARs activate gene transcription using PPAR-γ as an example. On ligand binding, the protein undergoes a conformational change that allows binding of transcriptional co-activators. In the absence of a ligand, the receptor remains bound to transcriptional co-repressors, resulting in target genes being silenced.



**Table 2. Genotype–phenotype correlations with some specific PPAR mutations illustrating the importance of these transcription factors in a variety of contexts [16]**

| Mutations in humans | Specific examples | Phenotype |
|---|---|---|
| PPAR-α | LEU162VAL | Susceptibility to hyperapobetalipoproteinaemia |
| PPAR-β/δ | SNPs (rs1053049) | |
| GLY482SER | Insulin resistance | |
| | Polymorphism 87T/C | Altered cholesterol metabolism |
| PPAR-γ | P115Q | Obesity |
| | 1-BP deletion 472A | |
| GLN286PRO | Colon cancer | |
| | PRO467LEU | Partial familial lipodystrophy type 3 |
| | 3-BP deletion/1-BP insertion NT553 | Insulin resistance |
| | Polymorphism PRO12ALA (13% of Caucasians) | Improved insulin sensitivity + lower BMI |

PRO467L, proline to leucine mutation; BP, base pair.
Data from Online Mendelian Inheritance in Man and Atlas of Genetics and Cytogenetics by Astarci and Banerjee.

are four domains within the protein: A/B (involved in transcriptional regulation), C (DNA binding), D (hinge region) and E/F (ligand binding). Two of these domains are highly conserved: one for DNA binding (DBD, made up of two zinc finger motifs and located at the N-terminal end of the protein; this allows specific interaction with the PPAR regulatory element common to all PPAR-responsive genes), and one for ligand binding (LBD, a structure containing α helices and β sheets, located at the C-terminus, that allows binding of natural and synthetic ligands to the PPAR). Activation of the receptor can be ligand-dependent [via the activation function 2 (AF2) domain at the C-terminus] or ligandindependent (via the AF1 domain at the N-terminus).

PPAR-γ2 has an additional 28 amino acids at its N-terminus, which enhances its ability for ligand-independent activation properties when compared with the γ1 isoform.

From transcription through to functioning protein, PPAR-γ is subjected to a number of complex processes and interactions. At the transcriptional level, these include epigenetic modifications such as promoter region methylation and histone acetylation. More recently, microRNAs have been shown to exert control over the stability and translation of PPAR mRNA [17,

18]. miR-128 has been identified as having direct interaction with PPAR-γ [19, 20]; for example, in a recent study of ischaemia–reperfusion (IR) injury in cardiac myocytes, the activation of PPAR-γ expression was increased by miR-128 inhibition and conversely, the reduction in apoptosis induced by miR-128 inhibition in IR-injured cells was blocked by the specific PPAR-γ inhibitor GW9662 [21].

Post-translational modifications are well described and include phosphorylation, acetylation, ubiquitination and sumoylation [12]. Phosphorylation of PPAR-γ can inhibit or increase its transcriptional activity depending on where that modification occurs. As an example, phosphorylation of serine 112 by MAP kinase at the N-terminus of the γ2 isoform or the corresponding serine 82 positioned at the N-terminus of the γ1 isoform reduces the transcriptional activity of PPAR-γ [5, 6, 22]. Conversely, phosphorylation at the same serine 112 by the cyclin-dependent kinase family members 5 and 9 (CDK5/9) increases PPAR-γ transcriptional activity [12].

The expression of PPAR-γ is regulated by a number of factors, including insulin, glucocorticoids and tumour necrosis factor a (TNF-α) in adipose tissue, with transfection studies in HepG2 cells, for example, showing insulin producing an almost 2-fold increase in the protein's transcriptional activity through mechanisms involving mitogen-activated protein kinase (MAPK) phosphorylation [5]. Insulin has also been shown to have a synergistic effect with ligand-dependent activation of PPAR-γ on the expression of aP2, a recognized target gene of PPAR-γ [23].

PPAR-γ1 is the predominant isoform in humans. Under normal physiological conditions, the γ2 isoform is limited to expression in adipose, but it can be induced in other tissues on exposure to a high-fat diet [12, 24]. The glomerulus is reported to be one of the major sites of PPAR-γ action within the kidney [14]. Quantitative mass spectrometry–based proteomics experiments on freshly isolated murine podocytes have previously identified a specific overrepresentation of both γ and α isoforms of the receptor [25], lending support to their relevance in this cell.

PPAR-γ is best known for its abilities to regulate pathways linked to adipocyte differentiation and metabolism [12]. However, it is now known that it is also important for podocyte function through the use of *in vitro* and cell-specific transgenic knockout (KO) models [26, 27]. This has provided an opportunity for research to focus on targeted therapy for disease involving GFB disruption.

## PPAR-γ ACTION THROUGHOUT THE BODY

PPAR-γ null mice die *in utero* due to placental defects (specifically due to the failure of trophoblastic differentiation) [28]; however, a whole body KO that can be rescued from embryonic lethality through genetic modification allowing PPAR-γ expression to be maintained only in trophoblastic cells [36] has been reported, showing severe lipodystrophy, insulin resistance and hypotension. Through the generation of cell specific transgenic

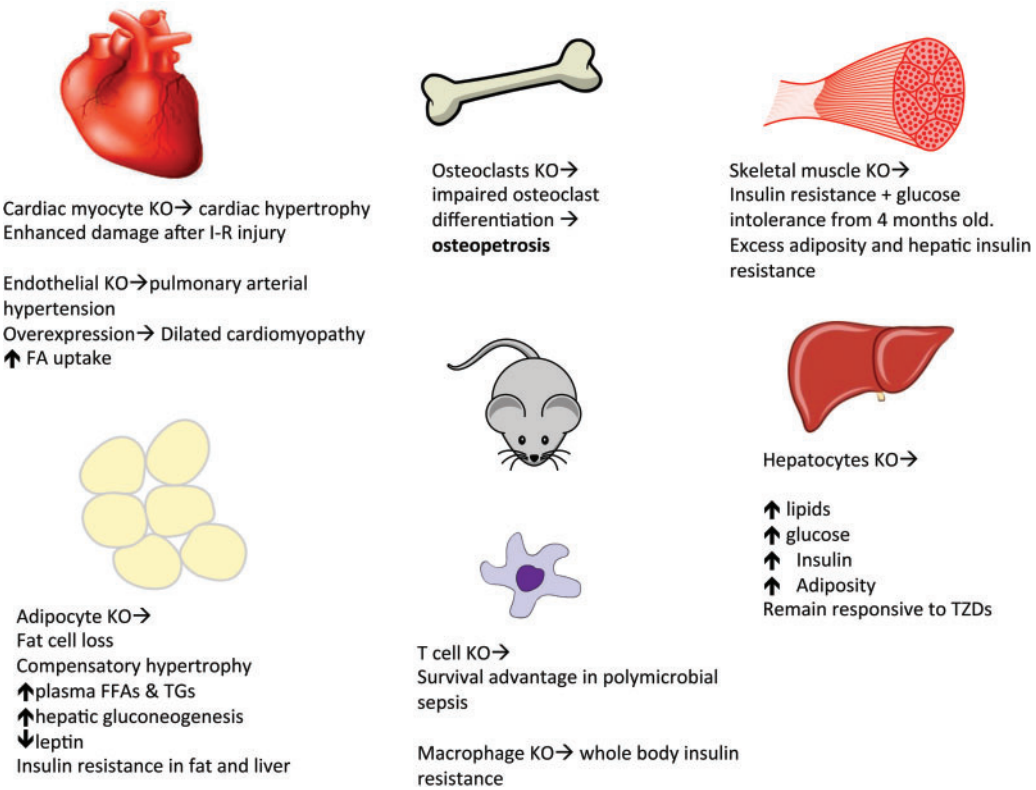


**FIGURE 2:** Tissue-specific knockout (KO) of PPAR-γ: skeletal muscle [29], hepatic [30], cardiac I-R (ischaemia–reperfusion injury) [31]; adipose [32]. Osteoclasts: Tie2Cre/flox mouse model (specific PPAR-γ gene deletion) [27], endothelial cells [33], T cells [34]. In the liver of the ob/ob mouse (genetically predestined to obesity) and the lipoatrophic mouse (AZIP) examples, KO of PPAR-γ has been shown to remedy the associated hepatic steatosis [35] but at the same time worsen the triglyceride clearance and total body insulin resistance.

mouse models it has become clear that PPAR gamma has important actions throughout the body (Figure 2).

The murine PPAR-γ heterozygote is protected from the hepatic steatosis induced by a high-fat diet and is also more insulin sensitive (an unexpected consequence of a functional decrease in gene expression, when considering that agonists of PPAR-γ enhance insulin sensitivity) [37, 38] and less susceptible to the colon cancer carcinogen azoxymethane (through mechanisms involving the suppression of β catenin and altered regulation of the β catenin/adenomatous polyposis coli pathway [39]). Heterozygosity for PPAR-γ has also been shown to have a protective effect in diabetic nephropathy [40].

In humans, loss-of-function/dominant-negative mutations in PPAR-γ cause partial lipodystrophy, insulin resistance and hypertension [41, 42].

## PPAR-γ IN THE KIDNEY

Using the Cre-lox system for investigating the effects of specific cell knock-down has provided insight into the role of PPAR-γ within the kidney (Figure 3).

## PPAR-γ IN THE PODOCYTE

Of particular interest is recent research suggesting a protective role for podocyte PPAR-γ in inflammatory crescentic glomerulonephritis [48]. In this study, the podocyte-specific PPAR-γ-deficient mice [generated by crossing the podocin-Cre mouse (which expresses Cre-recombinase exclusively in podocytes) with the B6.129S6-Ppargtm1.1Mgn/Mmmh strain on a C57BL6/J background] given nephrotoxin developed a more severe glomerulonephritis with a 2- to 3-fold increase in crescent formation compared with wild-type controls (littermates with no deletion of PPAR-γ alleles in any cells). This was associated with significantly accentuated periglomerular infiltration of T cells and macrophages and a 30% increase in mRNA expression of monocyte chemoattractant protein-1 and interleukin 6 (inflammatory cytokines) in the renal cortex. TZD treatment was less effective at alleviating the nephritis in the podocyte PPAR-γ KOs, showing that many of its effects are through this receptor.

In the same study, kidney biopsy specimens from patients with rapidly progressive glomerulonephritis were analysed, showing PPAR-γ to be absent from the nuclei of the cells forming crescents but present in normal glomerular cells.

Mechanistically, the induction of PPAR-γ by the nuclear factor erythroid 2-related factor (NRF2) has been described. The renal phenotypes of the podocyte-specific PPAR-γ KO and NRF2 KO are similar after exposure to a nephrotoxic insult. PPAR-γ in this study was shown to have reduced expression within the glomeruli of the NRF2 KO. In these mice, TZDs were able to alleviate the effects of the nephrotoxin-induced glomerulonephritis. In this model of acute inflammatory crescentic nephritis, TZDs work principally through PPAR-γ (in the

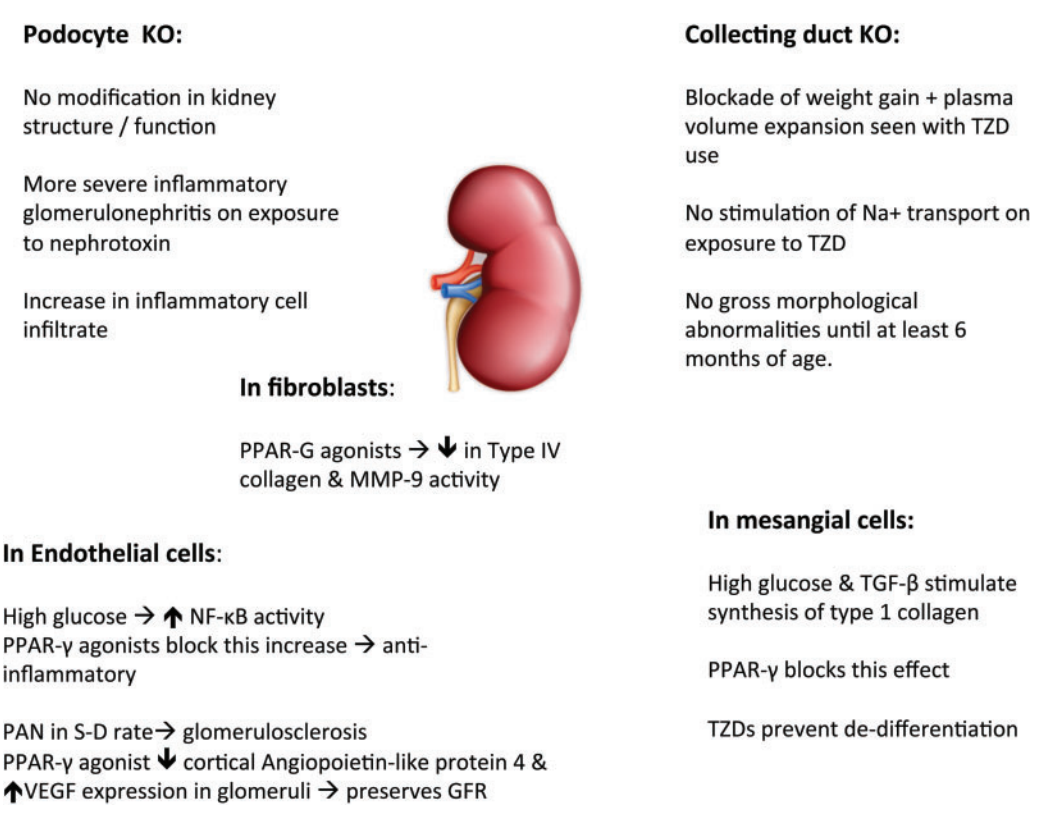


**FIGURE 3:** Collecting duct knockout → blockade of the body weight gain and plasma volume expansion associated with TZD use highlighting the importance of PPAR-γ-regulated fluid resorption in the distal nephron. These KO mice had no morphological abnormality by 6 months of age [43, 44]. Mesangial cells [45], endothelial cells [46] and pioglitazone reduces progression of glomerulosclerosis in Sprague–Dawley rats treated with PAN [10], fibroblasts [47] and PPAR-γ.

podocyte-specific KO, the TZDs had little effect) and therefore the NRF2–PPAR-γ pathway appears to play an important role in the prevention of oxidant-induced glomerular injury.

## ACTIVATING PPAR-γ THROUGH NATURAL AND SYNTHETIC LIGANDS

Synthetic agonists of PPAR-γ and endogenous agonists (such as fatty acid derivatives) have overlapping binding sites in the ligand binding pocket of the PPAR-γ LBD. Synthetic agonists compete with endogenous ligand for binding. More recently, it has become apparent that agonists can bind at an alternative site and facilitate a conformational change in the receptor that influences transcriptional activity. Understanding more about this particular mechanism may lead to the exploitation of synthetic agonists that have a more favourable side-effect profile than those currently in use (the TZDs). The TZDs do not display significant alternate binding site functional effects [49].

## TZD BENEFITS AND SIDE EFFECTS

TZDs are full agonists of PPAR-γ. They have strong insulin sensitizing actions and have been used very effectively to restore metabolic control in the treatment of type 2 diabetes [50]. The ability of the TZDs to enhance insulin sensitivity relies on their ability to modulate the activities of adipocytes and skeletal muscle cells. TZDs oppose the effects of TNF-α (pro-inflammatory cytokine) in adipocytes (probably through mechanisms involving the suppression of transcription factor NF-κB), as well as increasing the expression of the GLUT4 transporter, which is essential for the uptake of glucose into cells, and inducing the production of the insulin-sensitizing hormone adiponectin [12]. Through the enhancement of PI3-kinase activity and phosphorylation of AKT, the TZDs increase the utilization of glucose by skeletal muscle. They also inhibit the effects of resistin (an adipocyte-derived hormone that elevates blood glucose) [3].

At a cellular level, the TZDs have anti-inflammatory, anti-proliferative, anti-fibrotic and anti-apoptotic functions. Systemically they have an influence on haemodynamics and exert a mildhypotensive effect in both animals and humans [14, 51]. TZD-induced mitochondrial biogenesis has been shown to promote cell integrity and sustain survival in a number of cell types, including T lymphocytes and neurons [33, 52] (Figure 4).

Although tolerated by the majority of patients, clinical use of the TZDs has been hampered by an unfavourable side-effects profile with links to an increase in cardiovascular morbidity and mortality, carcinogenesis, hepatotoxicity and a reduction in bone mineral density [12]. Therefore, the focus on newer and more selective agents is of significant importance if their protective effects are to be exploited. Interestingly, anti-proteinuric agents including angiotensin receptor blockers such as irbesartan and telmisartan (characterized as selective PPAR-γ modulators in 2005 [34]) and angiotensin-converting enzyme inhibitors (used widely in the treatment of renal disease) are known to have partial PPAR-γ agonist activity [9, 53].

## TZD OFF-TARGET (PPAR-γ INDEPENDENT) EFFECTS

These are poorly understood, but involvement of the MAPKs and the glucocorticoid receptor (GR) has been suggested.

Treatment with a combination of TZD and dexamethasone (possibly due to the synergistic effects on GR phosphorylation) has been shown to protect podocytes from puromycin aminonucleoside (PAN)–induced injury (through improving cytoskeletal integrity and cell viability) [54]. It may therefore be that the TZDs exert an important influence on podocyte function and structure in part through this receptor.

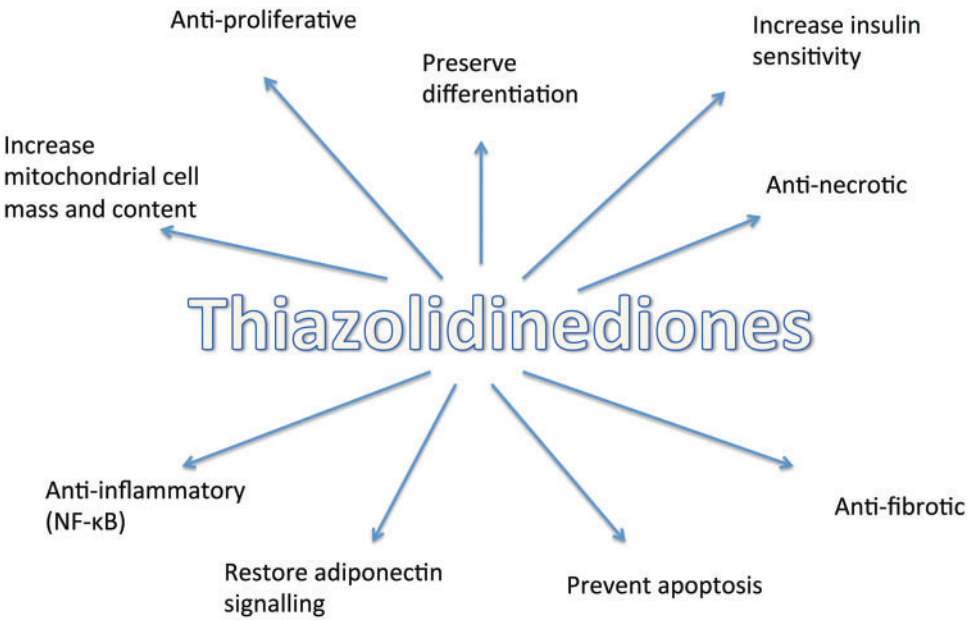


**FIGURE 4:** Effects of TZDs at a cellular level [11].

There is evidence that connects PPAR-γ with other receptors in the nuclear hormone family. The manipulation of these specific pathways may provide new targets for future therapeutic advance. For example, signalling pathways of the vitamin D receptor (VDR) and the PPARs are interconnected in a number of cancer cell lines including melanoma and human breast cancer cells (in the latter, PPAR-γ actively competes with the VDR for RXR binding/heterodimerization and suppresses vitamin D signalling) [55, 56]. The bile acid receptor farnesoid X (FXR), another nuclear hormone receptor, has been shown to regulate adipocyte differentiation in part through its interaction with PPAR-γ. FXR homozygous KO mice are resistant to the effects of rosiglitazone on adipocyte differentiation [57]. FXR ligands upregulate PPAR-γ mRNA in hepatic stellate cells and in rodent models of liver fibrosis, with this counter-regulatory action affording an anti-fibrotic effect [58].

MAPKs are a family of serine/threonine protein kinases involved in a wide range of vital cellular processes, including apoptosis, survival and motility [59]. Their activation has been implicated in the progression of various glomerulopathies. Rosiglitazone has been shown to deactivate several of the MAPKs (c-Jun/Erk1/2 and p38) [54]. Inhibition of p38 and Erk1/2 MAPKs in a rodent model of PAN-induced nephrotic syndrome and adriamycin nephropathy (in which podocyte damage is observed) has been linked to an improvement in podocyte health (through inhibition of actin reorganization) and a reduction in proteinuria [60].

## TZD RENAL AND SYSTEMIC ACTIONS

There is evidence that the TZDs reduce the progression of early diabetic nephropathy [61], the most common cause of renal failure in the developed world.

Using the example of the apolipoprotein E KO mouse that develops diabetes after exposure to STZ treatment, subsequent treatment with a PPAR-γ agonist markedly attenuates the hallmark changes within the glomeruli and tubules that are typical of nephropathy in this model. This effect is seen independently of changes in insulin, glucose and blood pressure reduction [62].

TZDs also appear to have protective roles in kidney disease more widely, for example, in non-diabetic glomerulosclerosis [63], focal segmental glomerulosclerosis [64], nephrotic syndrome [65], polycystic kidney disease [66] and in acute inflammatory crescentic glomerulonephritis [48] (Figure 5).

TZD protective roles span outside of renal disease and include beneficial effects in, for example, stroke [67] and skin cancer [68] (Table 3).

## TZD PODOCYTE EFFECTS

TZDs have been shown to increase the expression of PPAR-γ in podocytes as well as other glomerular and tubular cells at both the mRNA and protein levels [11, 69]. TZDs have also been shown to be podocyte protective in rodent models of nephropathy (aldosterone [70]/adriamycin [71]/puromycin aminonucleoside [11]) and glomerular capillary hypertension [72] (Figure 6).

Interestingly, PPAR-γ activation in the podocyte seems to be a key protective response after exposure to injury, with the upregulation in expression of PPAR-γ seen in a wide variety of kidney diseases [11, 73].

## THE FUTURE

Therapeutic advances and an improved understanding of PPAR-γ and its downstream molecular pathways have drawn

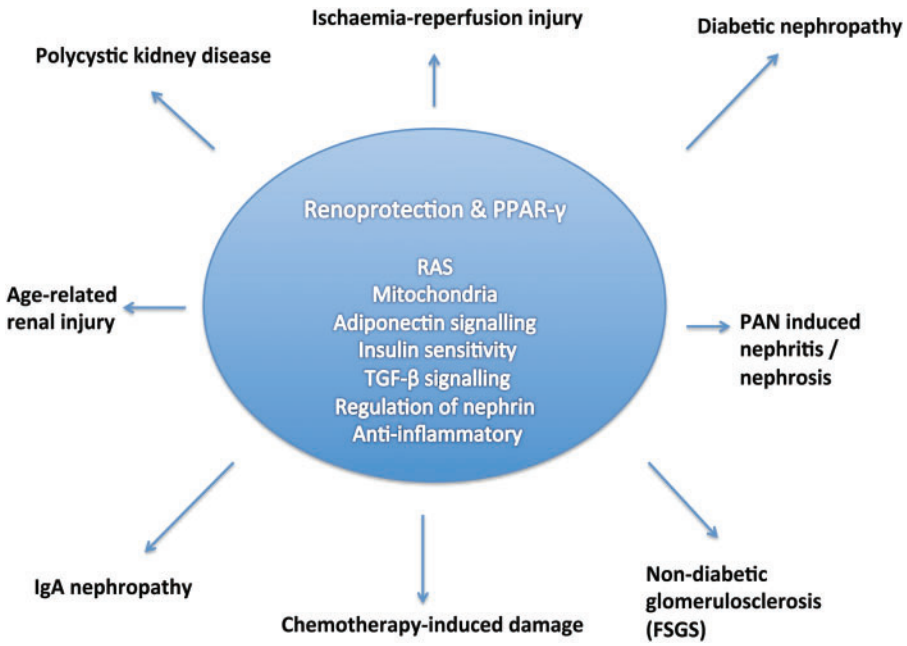


**FIGURE 5:** Outline of the protective mechanisms through which PPAR-γ has been suggested to work and the renal diseases influenced as a result. PAN, puromycin aminonucleoside; FSGS, focal segmental glomerulosclerosis; TGF, transforming growth factor; RAS, renin–angiotensin system.

**Table 3. The varying protective and damaging effects of PPAR-γ activation**

| System | Disease/model | Outcome | Reference |
|---|---|---|---|
| Central nervous system | Stroke | PPAR-γ agonist promotes cerebral protection | [83] |
| | Cerebral malaria | Improved neurological outcomes and survival | [84] |
| Vascular | Mouse model of hind limb ischaemia | PPAR-γ agonist promoted neovascularization | [85] |
| Gastrointestinal | Mouse model of IR injury | More severe disease in PPAR-γ-deficient mice, amelrioated by PPAR-γ ligand | [86] |
| Respiratory | Emphysema/mice exposed to chronic smoke | PPAR-γ downregulated in myeloid dendritic cells of smokers lungs | [87] |
| | Mice exposed to chronic smoke | PPAR-γ agonist reverses emphysema in mice | |
| Immune system | Polymicrobal sepsis | PPAR-γ activation induces T cell apoptosis → reduced survival | [88] |
| Renal | Type 2 diabetes | PPAR-γ agonists anti-albuminuric, produced a stabilization in eGFR and exerted a significant hypotensive effect | [89] |
| | FSGS | | [90] |
| | Non-diabetic renal disease (overweight adults) | | [91] |

IR, ischaemia–reperfusion injury; FSGS, focal segmental glomerulosclerosis.

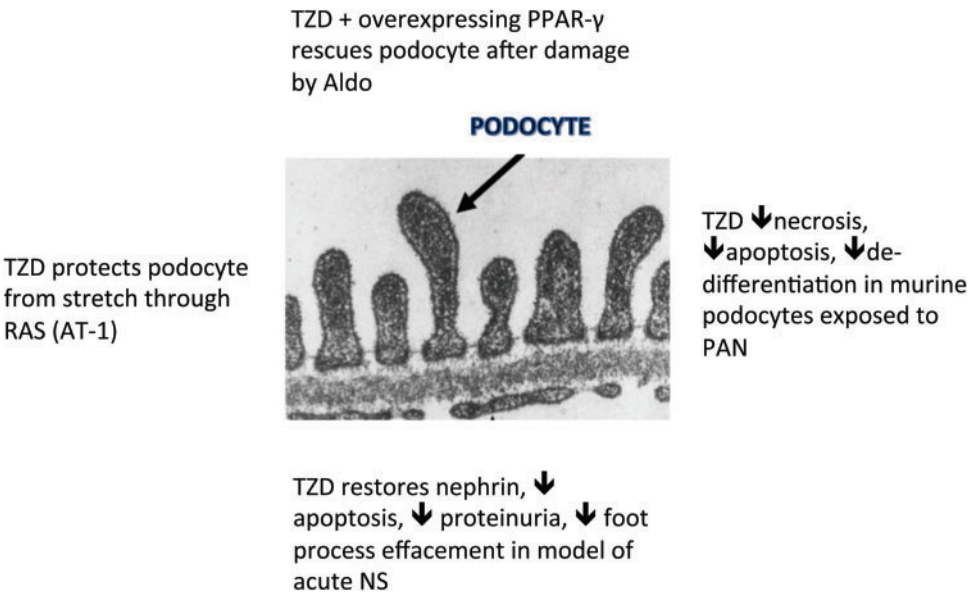


**FIGURE 6:** TZD podocyte-protective effects explained. After stretch: through RAS blockade [72]. In PAN nephritis: through restoration in balance of pro-apoptotic (caspase 3) and anti-apoptotic (Bcl-xl) molecules and reduction in pro-inflammatory TGF-β expression [11]. After damage by aldosterone [70]: overexpression of PPAR-γ/use of rosiglitazone, rescues podocytes through decreased ROS and maintenance of cell morphology (restores nephrin expression). Both are on-target effects (blocked by small interfering PPAR-γ RNA). In acute nephrosis [65], podocytes cause a decrease in the expression of nephrin, phosphorylated Akt and α-actinin 4 and an increase in apoptosis. PPAR-γ agonists given around the time of the injury produce a reversal of these effects as well as a reduction in proteinuria, a decrease in desmin and an improvement in foot process effacement [63].

attention to new PPAR-γ-based drugs, which are hopefully free of the side effects of the established TZDs (fluid retention, weight gain, cardiovascular morbidity, liver failure, cancer) [74–77]. A good example is the antidiabetic SR1664, which works completely separate from the typical transcriptional agonism associated with other PPAR-γ-mediated effects. SR1664 acts through blockade of the Cdk-5-mediated phosphorylation of PPAR-γ at serine 273 (a phosphorylation that is induced by obesity). It improves insulin sensitivity in insulin-resistant mice. It comes without the unwanted (TZD-associated) side effects of fluid retention and weight gain, including a lack of reduced bone cell mineralization of cells in culture [78]. By exploiting this phosphorylation pathway, there is perhaps new hope on the horizon for PPAR-γ-based drugs.

Targeting more than one of the PPAR isoforms simultaneously with agents such as the glitazars also provides opportunity. Aleglitazar, muraglitazar and saroglitazar target both PPAR-γ and PPAR-α and have been shown to improve insulin sensitivity and improve lipid profiles in the context of type 2 diabetes mellitus [79]. The use of muraglitazar, a strong agonist of PPAR-γ with moderate PPAR-α effects, was found to be associated with significant cardiovascular side effects and excess all-cause mortality [80] and as a result was never approved for clinical use. Saroglitazar has not demonstrated any of the

adverse side effects described in association with other PPAR-γ agonists, and although its long-term cardiovascular safety has not been established yet, it has been approved for use by the official medicines regulatory authority in India for the treatment of dyslipidaemia in type 2 diabetes [81, 82].

## CONCLUSIONS

PPAR-γ controls a large array of important cellular processes through the transcriptional regulation of specific gene cassettes. It has actions that are tissue and cell specific. The use of cell-specific transgenic models is helping us understand the complexities. It is clear that manipulation of PPAR-γ-related pathways (both on- and off-target) may be of great advantage to the podocyte in conditions of disease. We know that the TZDs, full agonists of the receptor, have a significant renoprotective effect in the context of diabetic nephropathy. The real challenges for the future surround understanding which are the key cells or tissues through which PPAR-γ exerts its actions and the development of new selective modulators of PPAR-γ with favourable side-effect profiles, and a focused research effort into the off-target mechanisms of its actions. Modulating this receptor may still have great therapeutic potential in preventing kidney disease.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract form.

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