Review Article

Pleiotropic actions of PPAR agonist: A potential therapeutic perspectives in the treatment of diabetic nephropathy

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. PPARα activators reduce the quantities of available fatty acids for triglyceride-rich very low-density lipoprotein synthesis in the liver. PPARα binds to a diverse set of ligands, namely, arachidonic acid metabolites (prostaglandins and leukotrienes), plasticizers and synthetic fibrate drugs such as bezafibrate, fenofibrate, clofibrate, and gemfibrozil. PPARγ agonists may also have therapeutic utility in the treatment of other conditions such as atherosclerosis, inflammation, cancer, and diabetic nephropathy. PPARδ plays a role in lipid metabolism, cholesterol efflux, and adipogenesis. In particular, diabetes is associated with the activation of enzymes that directly liberate ROS, including NAD(P)H oxidase. PPARα is expressed in proximal tubules and medullary thick ascending limbs where it is thought to be involved in the regulation of protein-degradation systems through maintenance of ATP homeostasis, control of fatty acid β-oxidation, and regulation of cytochrome P450 in proximal tubules. PPARγ is predominantly expressed in medullary collecting ducts and pelvic urothelium, and the latter site is potentially important for the putative link between PPARγ agonists and transitional cell cancer. The third isoform of PPAR and PPARβ/δ is also ubiquitously expressed in the kidney, with the highest levels observed in the proximal straight tubule in renal cortex and medulla. The review focuses on pleiotropic actions of PPAR agonist.

Keywords: Acute kidney injury, diabetes, nephropathy, peroxisome proliferator-activated receptors

Introduction

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes.[1] PPARs play essential roles in the regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, and protein)[2] and tumorigenesis[3] of higher organisms.[4,5]

Three types of PPARs have been identified: Alpha, gamma, and delta (beta):[4]

- α (alpha) - expressed in liver, kidney, heart, muscle, adipose tissue, and others[6]
- β/δ (beta/delta) - expressed in many tissues but markedly in brain, adipose tissue, and skin
- γ (gamma) - although transcribed by the same gene, this PPAR through alternative splicing is expressed in three forms:
  - γ1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas, and spleen
  - γ2 - expressed mainly in adipose tissue (30 amino acids longer than γ1)
  - γ3 - expressed in macrophages, large intestine, and white adipose tissue.

The first PPARα was discovered during the search of a molecular target for a group of agents then referred to as peroxisome proliferators, as they increased peroxisomal numbers in rodent liver tissue, apart from improving insulin sensitivity.[7] These agents pharmacologically related to the fibrates were discovered in the early 1980s. When it turned out that PPARs played a much more versatile role in biology, the agents were in turn termed PPAR ligands. The best-known PPAR ligands are the thiazolidinediones (TZDs), see below for more details. After

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PPARδ (delta) was identified in humans in 1992,[8] it turned out to be closely related to the PPARβ previously described during the same year in other animals (Xenopus). The name PPARδ is generally used in the US, whereas the use of the PPARβ denomination has remained in Europe where this receptor was initially discovered in Xenopus.

PPARs belong to the nuclear hormone receptor superfamily, and three different subtypes have been identified, PPAR, PPAR (also called PPAR or NUC-1 or FAAR), and PPAR and these receptors have been found in teleosts, amphibians, rodents, and humans.[8-14] Alternate promoter usage and splicing occur and three PPAR variants have been characterized PPAR1, 2, and 3. PPAR2 has 30 additional N-terminal amino acids. A third promoter in the human sequence encodes a protein, PPAR3.[14] The PPAR subtypes are encoded by distinct single-copy genes and have a structure characteristic of the nuclear hormone receptors. Each receptor has an N-terminal "A/B" domain that has a ligand-independent activation function (AF) and is poorly conserved between the isoforms. The "C" domain encodes the DNA binding region of the receptor, is highly conserved, includes two zinc finger-like structures with helical DNA binding motifs, and is followed by the "D" or hinge region. The C-terminal ligand-binding domain (LBD), the "E/F" domain, contains the ligand-dependent AF-2 and is also important for retinoid X receptor heterodimerization. The ligand-binding domains (LBD) are highly conserved, and the mouse PPAR2 LBD sequence is 70% and 68% similar to mouse PPAR and PPAR LBDs, respectively.[15] The rat and mouse PPAR proteins share 92% identity with the human receptor. The rat and mouse PPAR are 91% and 92% homologous with the human PPAR amino acid sequence. Rat and mouse PPAR1 and 2 have 95–98% homology with the human receptor.[16]

Role of PPARα agonist

PPARα was cloned early in the 1990s. It plays an important role in the oxidation of fatty acids in the liver. Receptor activation stimulates fatty acid oxidation such as in fasting, which is a crucial adaptive response to the nutritional challenge. PPARα is highly expressed in tissues with high rates of fatty acid catabolism. This receptor regulates genes that control fatty acid uptake, causes activation of acyl CoA esters and degradation by mitochondrial β-oxidation pathways. PPARα activators reduce the quantities of available fatty acids for triglyceride-rich very low-density lipoprotein synthesis in the liver. Hence, the physiological role of PPARα receptor is to sense the total flux of dietary fatty acids in key tissues. PPARα binds to a diverse set of ligands, namely, arachidonic acid metabolites (prostaglandins and leukotrienes), plasticizers, and synthetic fibrate drugs such as bezafibrate, fenofibrate, clofibrate, and gemfibrozil. More recent thioisobutyric acid compounds (GW 7647 and GW 9578) show excellent selectivity for PPARα receptors. Recently reported LY518674 is a novel selective PPARα agonist.[17] Given that these agents have exhibited improved insulin action and glucose utilization in both high fats fed C57BL6 mice and obese zucker rats, and the data suggest that PPARα ligands can reduce insulin resistance without significant effects on adipose mass accumulation.[18] Another study has been suggested that the agent ANGPTL4 could exert distinct effects on lipid and glucose metabolism mainly through PPAR signaling but not through LXR because ANGPTL4 mRNA was upregulated by PPARα, PPARγ, and PPARβ/δ agonists. PPARα plays an important role during fasting through the ligand-dependent transcriptional activation of target genes, while PPARγ regulates systemic insulin signaling. However, the exact roles of ANGPTL4 in regard to physiology and pathology in humans remain uncertain.[19] PPARα agonists such as fibrates are not only effective hypoglycemic agents but also lower low-density lipoprotein cholesterol and triglycerides and raise high-density lipoproteins, thus offering protection against increased coronary morbidity and mortality which is seen in type 2 diabetes.[20]

Role of PPARγ agonist

PPARγ is a pivotal transcription factor in the regulation of adipocyte gene expression and differentiation. The regulation of adipocyte differentiation by PPARγ involves a coordinated signaling cascade with other families of transcription factors. In addition to adipogenic effects, PPARγ has been shown to be an important regulator of target genes involved in glucose and lipid metabolism. PPARγ agonists are efficacious antidiabetic agents. PPARγ agonists may also have therapeutic utility in the treatment of other conditions such as atherosclerosis, inflammation, and cancer. Ligand studies have shown numerous naturally occurring fatty acids, eicosanoids, prostaglandins, and their metabolites to be weak endogenous activators of PPARγ. PPARγ exhibits a modest preference for essential polyunsaturated fatty acids (PUFAs) including linoleic, linolenic, arachidonic, and eicosapentaenoic acids. Thus, PPARγ may serve as a generalized fatty acid sensor that couples changes in overall PUFAs' concentration with the target genes associated with lipid and glucose homeostasis. Clinical benefits of PPARγ agonists in treating type-2 diabetes have been clearly demonstrated, but the problem associated with the current generation of glitazone drugs is that they are associated with undesirable side effects such as weight gain and edema.[21,22] The treatment of type-2 diabetes is the most widely studied therapeutic utility for a PPARγ agonist. PPARγ agonists reduce plasma glucose, lipid, and insulin levels in type-2 diabetes. TZDs are the new class of drugs used in the treatment of type-2 diabetes. Recent advances include the discovery of novel genes that are regulated by PPARγ, which helps explain how activation of this adipocyte predominant transcription factor regulates glucose and lipid homeostasis.

TZDs suppress insulin resistance in adipose tissue in addition to skeletal muscle and liver, which contain a low concentration of PPARγ. Adipose tissues function as an endocrine organ. PPARγ agonists ameliorate hyperglycemia, by reversing lipotoxicity-induced insulin resistance (Figure 1).

Data from patients with type-2 diabetes mellitus and preclinical studies also demonstrate that PPARγ agonists function as "adipose remodeling factors" that redistribute lipids from insulin-resistant, lipolytic visceral-fat depots into subcutaneous fat that contains small, newly differentiated, insulin-responsive adipocytes. PPARγ ligands regulate the expression of several other genes that enhance glucose metabolism in the adipocyte, including those which encode the insulin-responsive glucose transporter GLUT4, GLUT2, and c-Cbl associating protein (crucial for GLUT4 translocation to the surface).

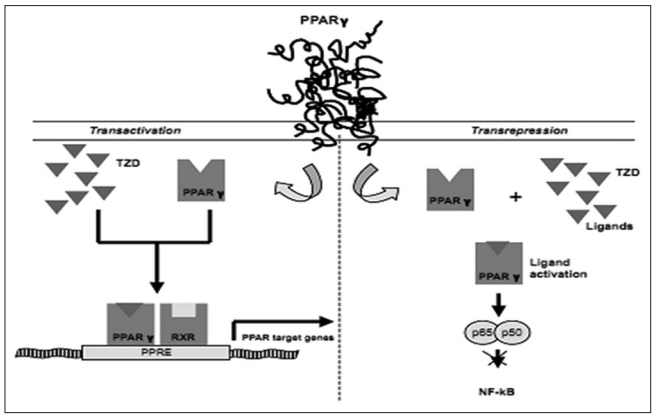


Figure 1: Molecular mechanisms of thiazolidinediones (TZDs). In transactivations, PPARγ is a nuclear receptor that acts as a transcription factor on activation. TZDs can active PPARγ. On ligand binding, the PPAR forms a heterodimer with the retinoid X receptor and they bind to specific peroxisome proliferator response elements on a number of key target genes involved in the carbohydrate and lipid metabolism. In transespression, PPARs can repress gene transcription of other pathways, such as nuclear factor-kB (NF-kB)

By this way, they increase glucose uptake into tissue and decrease overall glucose. Overexpression of 11β-HSD1 (11β-hydroxysteroid dehydrogenase 1) in adipocytes cause insulin resistance, suggesting that reduction of adipocyte 11β-HSD1 might promote insulin sensitivity, either by reducing glucocorticoid-induced gene expression in the adipocyte or by reducing adipocyte secretion of glucocorticoids. Any or all of these effects might contribute to the smaller adipocyte size that is associated with PPARγ activation. It has been reported that smaller adipocytes typically have greater insulin sensitivity, take up more glucose, and have lower rates of lipolysis compared to large adipocytes.[23,24] In addition to the improvement in glycemic control, the glitazones have a beneficial effect on many of the traditional as well as the new risk factors and can help in preventing or lessening the impact of the cardiovascular consequences of type 2 diabetes. They have been shown to lower the levels of atherogenic dyslipidemia, lower blood pressure (BP) as well as visceral obesity, lessen the levels of the pro-inflammatory and prothrombotic cytokines and adipokines as well as increase the levels of the antiatherogenic adiponectin.[25] Activation of PPARγ2 results in an increase in the sensitivity of both the liver to insulin-mediated suppression of hepatic glucose production and insulin-mediated skeletal muscle glucose uptake.[26] PPARα and PPARγ have been reported to upregulate nitric oxide synthase and stimulate NO release, which is beneficial to counteract endothelial dysfunction commonly present in patients with metabolic syndrome, especially obesity, insulin resistance, and type 2 diabetes.[27]

Role of PPARδ agonist

Understanding the biological function of PPARδ, however, has been impeded due to its ubiquitous expression, the absence of potent and selective ligands, and the lack of connection of clinical disorders. However, growing evidence suggests that PPARδ plays a role in lipid metabolism, cholesterol efflux, adipogenesis, colon cancer, bone metabolism, embryo implantation, and development of brain and skin.[28,29]

PPAR-a and PPAR-g agonists are widely used in diabetes. In addition to their effects on lipid and glucose homeostasis, these agents have been postulated to have independent renoprotective actions. In this study, they assess the efficacy of the PPAR-a agonist, gemfibrozil, the PPAR-g agonist rosiglitazone and the non-thiazolidinedione PPAR-a/g agonist, compound 3q, on kidney structure and function in streptozotocin-treated apolipoprotein E knockout mice. They showed that the increase in albuminuria and the decline in kidney function associated with diabetes in this model were also attenuated by each of these agents, with no superiority observed among various treatment groups.[30]

Clinical use of these agents has improved our understanding of the role of one subtype, PPAR, in diabetes mellitus.[31] Administration of TZDs to insulin resistant or type 1 diabetic rats ameliorates albuminuria, glomerular matrix deposition, glomerulosclerosis, and tubulointerstitial fibrosis, characteristic changes of diabetic nephropathy.[31,32] *In vitro*, TZDs also prevent high glucose-induced mesangial and tubulointerstitial cell injury.[33,34] In human study, rosiglitazone is shown to reduce urinary albumin excretion in type 2 diabetes.[35] These renoprotective effects of TZDs are supposed to be due to its anti-inflammatory properties. In addition, Tang *et al*. have recently reported that AGEs stimulate renal tubular expression of adhesion molecule and chemokine that together may account for the transmigration of inflammatory cells into the interstitial space during diabetic tubulopathy. Such pro-inflammatory phenotype may be partially modified by PPAR ligation through STAT-1 (signal transducer and activator of transcription-1) inhibition independent of NF-B transcriptional activity and mitogen-activated protein kinase (MAPK) signalling (Figure 2).[36]

PPARγ modulates numerous effectors of ECM accumulation. TZDs are synthetic ligands of PPARγ, which is involved in many important physiological processes, including adipose differentiation, lipid and glucose metabolism, energy homeostasis, cell proliferation, inflammation, reproduction, and renoprotection.[38] TZD prevented the increase of transforming growth factor (TGF)-b and increase of ECM in cultured human mesangial cells, and both mesangial cell and fibroblast proliferation *in vitro* were inhibited by PPARγ agonists. TGF-b effects in fibroblasts were blocked by TZDs through inhibition of the downstream Smad signaling pathway. PPARγ also interacts with the renin-angiotensin system. In a number of studies, TZDs decreased activation of the renin-angiotensin system components in both adipocytes and vascular smooth muscle cells. Experimental knockout of PPARγ in macrophages resulted in increased expression of the angiotensin II type 1 receptor and greater migratory response to exogenous angiotensin.[39]

PPARs in the kidney

In the kidney, PPARα is expressed in proximal tubules and medullary thick ascending limbs where it is thought to be involved in the regulation of protein-degradation systems through maintenance of ATP homeostasis, control of fatty acid β-oxidation, and regulation of cytochrome P450 in proximal tubules. PPARγ is predominantly expressed in medullary collecting ducts and pelvic urothelium, and

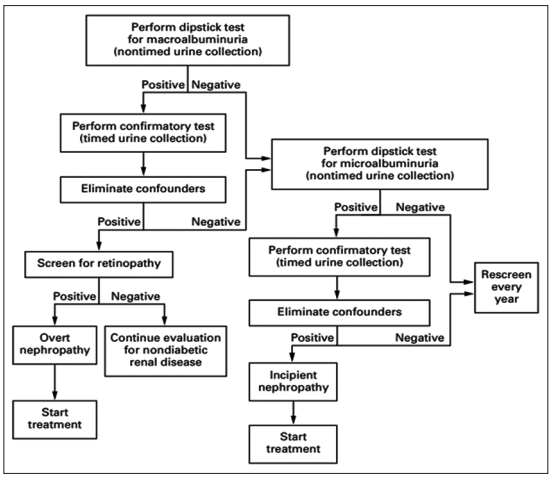


Figure 2: Screening of nephropathy patients in type 2 diabetes[37]

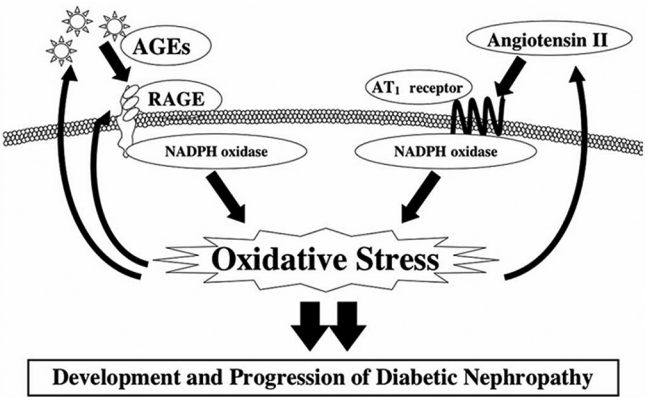
the latter site is potentially important for the putative link between PPARγ agonists and transitional cell cancer. Studies using more specific antibodies suggest that lower level PPARγ expression is observed in glomeruli, proximal and distal tubules, the loop of Henle, medullary collecting ducts, and intima-media of renal vasculature. The third isoform of PPAR and PPARβ/δ is also ubiquitously expressed in the kidney, with the highest levels observed in the proximal straight tubule in renal cortex and medulla.[39]

Renal disease in diabetic patients is characterized by oxidative modification of proteins, lipids, carbohydrates, and DNA associated with increased production of oxidants or reactive oxygen species apoE (ROS) that exceeds local antioxidant capacity. In particular, diabetes is associated with the activation of enzymes that directly liberate ROS, including NAD(P)H oxidase.[40,41] The potential importance of this pathway is illustrated by findings demonstrating that pharmacological inhibition of NAD(P)H oxidase with apocynin prevents mesangial matrix expansion seen in experimental diabetic nephropathy.[42] In addition, gemfibrozil attenuated gene expression of each of NAD(P)H oxidase subunits including Cybb, Ncf1, and Rac1, the genes encoding gp91phox, p47phox, and Rac-1, respectively. TGF-β-induced oxidative stress in mesangial cells can also be attenuated by PPARα agonist and clofibrate.[43] Selective mitochondrial antioxidants, such as mitoQ, have been shown to have renoprotective actions in experimental diabetes.[44]

Pathophysiology of Diabetic Nephropathy

The natural history of diabetic nephropathy differs between Type 1 and 2 patients. If untreated, approximately 80% of type 1 diabetic patients will develop overt albuminuria (UAER >200 g/min) over a 15-year period. Of these patients, 50% will develop ESRD over the ensuing 10 years. In Type 2 diabetes, if no treatment is initiated, up to 20–40% of patients will progress to overt albuminuria and 20% of those with overt albuminuria will develop ESRD over the next 20 years. When comparing two types of diabetes, diabetic nephropathy is less common (5–10%) in Type 2 diabetes than in Type 1 diabetes (30–40%) although the total number of patients with ESRD is similar for the two diabetic populations.[45]

Diabetic nephropathy is a leading cause of ESRD and accounts for disabilities and the high mortality rate in patients with diabetes. Development of diabetic nephropathy is characterized by glomerular hyperfiltration and thickening of glomerular basement membranes, followed by an expansion of extracellular matrix in mesangial areas and increased UAER. Diabetic nephropathy ultimately progresses to glomerular sclerosis associated with renal dysfunction.[45] Further, it has recently been recognized that changes within tubulointerstitium, including proximal tubular cell atrophy and tubulointerstitial fibrosis, are also important in terms of renal prognosis in diabetic nephropathy.[11-15] Such tubular changes have been reported to be the dominant lesion in about one-third of patients with Type 2 diabetes. It appears that both metabolic and hemodynamic factors interact to stimulate the expression of cytokines and growth factors in glomeruli and tubules from the diabetic kidney.[45] Numerous studies have demonstrated that the RAS is an important target for both metabolic and hemodynamic pathways in diabetic nephropathy. So far, angiotensin-converting enzyme inhibitors and an angiotensin II (Ang II) type I receptor blockers (ARBs) have been widely used as major therapeutic agents for diabetic nephropathy in both Type 1 and 2 diabetic patients. The renoprotective effects of these agents are largely ascribed to its BP-lowering properties; however, a recent clinical study suggests the pleiotropic effects of the RAS inhibitors, i.e., beyond BP-lowering effects and on diabetic nephropathy. Indeed, it has been shown that irbesartan, an ARB, significantly prevents the progression of diabetic nephropathy in Type 2 diabetic patients, compared with a calcium channel blocker, amlodipine, with an equipotent BP-lowering property.[45] Further, the RAS stimulates the production of several growth factors and cytokines. The deleterious actions of Ang II on diabetic nephropathy are mediated partly by TGF-, a fibrogenic factor.[46-48] In addition, other factors such as connective tissue growth factor, vascular endothelial growth factor, and platelet-derived growth factor in relation to intracellular second messenger molecules such as MAPK, NF-kB, and PKC have also been linked to the RAS, thereby implicated in the development and progression of diabetic nephropathy.[49-54] It is also reported that high glucose, through various mechanisms such as increased production of oxidative stress and AGEs, activates the RAS, being involved in diabetic nephropathy as well.[55]



Treatment with PPARγ agonists is limited by several common adverse effects, including substantial weight gain and fluid retention. This PPAR

research is thought to be the result of upregulation of the epithelial sodium channel in the kidney, promoting fluid retention. In addition, activation of PPARγ results in activation of the sympathetic nervous system increased endothelial permeability[39] and increased renin expression. Podocytes clearly express PPAR; however, more importantly, podocyte injury may be attenuated following treatment with PPAR agonists, both *in vitro* and *in vivo*. For example, PPARα agonists are also able to increase gene expression of the key slit-pore protein, nephrin, in diabetic nephropathy, potentially contributing to their antiproteinuric actions. PPARγ agonists also affect nephrin gene transcription. Indeed, in cultured podocytes, TZDs are able to directly reduce apoptosis and injury and improve podocyte differentiation. Similarly, in an immune model of progressive nephropathy, passive Heymann nephritis, the PPARγ agonist, and pioglitazone had an antiproteinuric effect, possibly through transcriptional regulation of nephrin.[39]

The potential actions of PPARδ agonists in the diabetic kidney have only been recently explored. In streptozotocin-induced diabetes, the expression of PPARδ is increased in the kidney, associated with the development and progression of renal damage. By contrast, the selective PPARδ agonist GW0742 reduces albuminuria, glomerular mesangial expansion, renal inflammation, and collagen accumulation, without significantly affecting blood glucose levels.[39] Activation of the PPARδ receptor is thought to alter the circulating lipid profile by enhancement of fat oxidation in skeletal muscle. PPARδ knockout mice are also insulin-resistant/glucose intolerant, although this may reflect lipotoxicity rather than a direct effect on insulin sensitivity. PPARδ agonists may also have direct effects on a number of critical pathways that are implicated in the development and progression of diabetic kidney disease, over and above action on metabolic control. Some data suggest that PPARδ is involved in the regulation of apoptosis in response to renal injury.[56] Deficiency of PPARδ increases susceptibility to ischemic injury in the kidney, while selective agonists of PPARδ protect against ischemic acute renal failure. Certainly, hypoxia is known to be an important factor in the pathogenesis of diabetic kidney disease,[56] implying that this effect may be important in the diabetic kidney. In addition, the expression of PPARδ is increased in the diabetic kidney.

All three PPARs are expressed in the kidney. PPARγ mRNA has been demonstrated in the medullary collecting ducts and pelvic urothelium of the kidney, as well as in isolated glomeruli and cultured mesangial cells.[57]

PPARα and γ1, but not γ2, the protein was detected in kidney tissue by immunoblot analysis, while immunohistochemical analysis revealed PPARα and γ1 proteins in the nuclei of mesangial cells and epithelial cells in glomeruli, proximal and distal tubules, the loop of Henle, medullary collecting ducts, and the intima/media of renal vasculatures. Large amounts of PPARα have also been detected in proximal tubular cells, and renal lipid metabolism is highly regulated by PPARα. In contrast to PPARα, PPARγ protein is highly expressed in the nephron segment, predominantly in collecting ducts, implicating PPARγ in systemic water and sodium retention.[57]The activation of PPARα by fenofibrate would improve diabetes and its renal complications in Type II diabetes mellitus. Male C57 BLKS db/db mice and db/m controls at 8 weeks of age were divided to receive either a regular diet chow (db/db, $n = 8$; db/m, $n = 6$) or a diet containing fenofibrate (db/db, $n = 8$; db/m, $n = 7$). Mice were followed for 8 weeks. Fenofibrate treatment dramatically reduced fasting blood glucose ($P < 0.001$) and HbA1c levels ($P < 0.001$) and was associated with decreased food intake ($P < 0.01$) and slightly reduced body weight. Fenofibrate also ameliorated insulin resistance ($P < 0.001$) and reduced plasma insulin levels ($P < 0.05$) in db/db mice. Hypertrophy of pancreatic islets was decreased and insulin content markedly increased ($P < 0.05$) in fenofibrate-treated diabetic animals.[58] In addition, fenofibrate treatment significantly reduced urinary albumin excretion ($P < 0.001$). This was accompanied by dramatically reduced glomerular hypertrophy and mesangial matrix expansion. Furthermore, the addition of fenofibrate to cultured mesangial cells, which possess functional active PPARα, decreased Type I collagen production. Taken together, the PPARα agonist fenofibrate dramatically improves hyperglycemia, insulin resistance, albuminuria, and glomerular lesions in db/db mice. The activation of PPARα by fenofibrate in mesangial cells may partially contribute to its renal protection. Thus, fenofibrate may serve as a therapeutic agent for type II diabetes and diabetic nephropathy.[59] Microalbuminuria and hypertension are risk factors for diabetic nephropathy. Blockade of the renin-angiotensin system slows the progression to diabetic nephropathy in patients with Type 1 diabetes, but similar data are lacking for hypertensive patients with Type 2 diabetes. One study evaluated the renoprotective effect of the angiotensin-II receptor antagonist irbesartan in hypertensive patients with Type 2 diabetes and microalbuminuria.[60]

Conclusion

The increased incidence of diabetic nephropathy has become a major health problem worldwide. As discussed in this review, PPARs comprise a subfamily of nuclear receptors and transcription factors that play critical roles in modulating insulin resistance, hypertension, dyslipidemia, obesity, hypertension, and inflammation. Given the close relationship between PPAR activity and these metabolic alterations, PPAR agonists are promising therapeutic agents for diseases including Type 2 diabetes, obesity, hypertension, hyperlipidemia, and atherosclerosis. Fibrate PPARα agonists and TZD PPARγ agonists are already used successfully as clinically effective hypolipidemic drugs and insulin sensitizers. PPARβ/δ agonists may provide additional insulin and lipid modulators through their effects on skeletal muscle. In addition, there is an increasing evidence suggesting that all three PPARs contribute to the metabolic control of renal function and are involved in the pathogenesis of diabetic nephropathy. PPARα agonists are available as optional therapeutic agents for nephropathy in Type 2 diabetes. In the near future, both PPARγ and PPARβ/δ agonists might be added to that strategy with further evidence that these agents have a proven renoprotective effect in diabetic animals and patients.

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