PPARs and the kidney in metabolic syndrome

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Am J Physiol Renal Physiol 294: F1032–F1047, 2008. First published January 30, 2008; doi:10.1152/ajprenal.00152.2007.—The metabolic syndrome (MetS) is defined by a set of metabolic risk factors, including insulin resistance, central obesity, dyslipidemia, hyperglycemia, and hypertension for type 2 diabetes and cardiovascular disease. Although both retrospective and prospective clinical studies have revealed that MetS is associated with chronic renal disease, even with a nondiabetic cause, the cellular and molecular mechanisms in this association remain largely uncharacterized. Recently, increasing evidence suggests that peroxisome proliferator-activated receptors (PPARs), a subgroup of the nuclear hormone receptor superfamily of ligand-activated transcription factors, may play an important role in the pathogenesis of MetS. All three members of the PPAR nuclear receptor subfamily, PPARα, -β/δ, and -γ, are critical in regulating insulin sensitivity, adipogenesis, lipid metabolism, inflammation, and blood pressure. PPARs have also been implicated in many renal pathophysiological conditions, including diabetic nephropathy and glomerulosclerosis. Ligands for PPARs such as hypolipidemic PPARs activators, and antidiabetic thiazolidinedione PPARγ agonists affect not only diverse aspects of MetS but also renal disease progression. Emerging data suggest that PPARs may be potential therapeutic targets for MetS and its related renal complications. This review focuses on current knowledge of the role of PPARs in MetS and discusses the potential therapeutic utility of PPAR modulators in the treatment of kidney diseases associated with MetS.

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modulating PPAR activity have also attenuated or even prevented CKD. This review examines the current knowledge about the physiological function of each PPAR isoform. It highlights the current understanding of the pathogenic roles of the three PPAR subtypes in MetS and the possible mechanisms underlying the association between MetS and CKD. Finally, the clinical utility of PPAR ligands as potential therapeutic agents in the syndrome and associated kidney disease is also discussed, with particular focus on the treatment of diabetic nephropathy.

**PPARs and MetS**

**Overview of PPAR family.** PPARs belong to the nuclear hormone-activated receptor and transcription factor superfamily. Three different PPAR subtypes identified and characterized include PPARα (NR 1C1), PPARβ/δ (NR 1C2), and PPARγ (NR 1C3) (33, 44, 64). Similar to other nuclear receptors, PPARs have four major functional domains: an NH2-terminal ligand-independent transactivation domain (A/B domain), a DNA-binding domain (DBD; or C domain), a cofactor docking domain (D domain), and a COOH-terminal E/F domain that includes the ligand binding domain and the ligand-dependent transactivation domain (AF2 domain) (Fig. 1) (62). The function of PPAR isoforms is tightly controlled by complex signaling pathways under physiological conditions, and dysregulation of these proteins may ultimately lead to many metabolic diseases including insulin resistance, obesity, hypertension, dyslipidemia, and steatosis. The actions of PPARs are mainly through a ligand-dependent transactivation mechanism, modulating transcriptional activity of their target genes (Fig. 1). Similar to other nuclear receptors in the thyroid/retinoid family (class II), PPAR forms a heterodimer with retinoid X receptor-α, which then binds to a specific cis-element, PPRE (DR-1), in the promoter region of PPAR target genes. Binding of the nuclear receptor heterodimer to the PPRE activates transcription of PPAR target genes (64). To date, most of the genes under direct control of PPARs are found to be involved in energy homeostasis, insulin sensitivity, and lipid metabolism.

PPARs can also regulate gene transcription via a ligand-dependent transrepression mechanism by interfering with other transcription pathways (Fig. 1), including NF-κB, STAT, C/EBP, and AP-1, thereby repressing the expression of cytokine-responsive genes, inhibiting cell recruitment and migration of inflammatory cells, and attenuating vasoconstriction and thrombosis (62). The cell type and subtype specificity is suggested to largely depend on the recruitment of multisubunit cofactor complexes involved in modification of histones.

Increasing recognition is being given to several proteins acting as coactivators or corepressors to mediate the ability of nuclear receptors initiating or suppressing the transcription process. These proteins interact with nuclear receptors in a ligand-dependent manner. In the unliganded state, the heterodimerized nuclear receptor associates with multicomponent corepressors containing histone deacetylase activity, such as nuclear receptor corepressor (NCoR) and the silencing mediator for retinoid and thyroid hormone receptor (SMRT), thereby inhibiting transcription. In contrast, coactivators such as steroid receptor coactivator (SRC)-1 and the PPAR binding protein (PBP) with histone acetylase activity initiate a sequence of events that induces the gene transcription process on ligand binding (96) (Fig. 1). For example, the molecular pathway by which PPARγ represses the transcriptional activation of inflammatory response genes may involve ligand-dependent SUMOylation of the PPARγ ligand-binding domain, which targets PPARγ to NCoR-histone deacetylase-3 (HDAC3) complexes on inflammatory gene promoters. This situation, in turn, prevents recruitment of the ubiquitylation/19S proteasome machinery that normally mediates the signal-dependent removal of corepressor complexes required for gene activation. As a result, NCoR complexes are not cleared from the promoter, and target genes are maintained in a repressed state. This mechanism provides an explanation for how an agonist-bound nuclear receptor can be converted from an activator of transcription to a promoterspecific repressor of NF-κB target genes that regulate immunity and homeostasis (144).

![Fig. 1. Schematic representation of the mode of action and functions of peroxisome proliferator-activated receptor (PPAR)α, -β/δ, and -γ.](http://ajprenal.physiology.org/)
In addition to availability of the ligands, recent emerging evidence demonstrates that PPAR receptor activity is post-translationally modified by its phosphorylation status. PPARs can be phosphorylated by several kinases (PKA, PKC, MAPKs, and AMPK), which affect their activity in a ligand-dependent or -independent manner according to the isoform and cellular context, thereby resulting in changes in ligand affinity, DNA binding, recruitment of transcriptional cofactors, and proteasome degradation (37). In addition, PPARs may also exert their biological effect independently of binding to DNA (46, 126), although the precise nongenomic mechanism is not completely understood.

Although the three PPAR subtypes have many aspects of shared biology, each isoform has unique nonoverlapping patterns of tissue distribution, ligand selectivity, and biological effects. In general, PPARα regulates genes important for lipid uptake and fatty acid catabolism in the liver, thereby diminishing circulating triglyceride and increasing HDL-cholesterol levels. PPARβ/δ controls the expression of key genes involved in fatty acid oxidation and energy uncoupling in skeletal muscle, which leads to decreased plasma triglyceride levels, increased HDL-cholesterol concentrations, and a lean phenotype. Unlike PPARα and PPARβ/δ, PPARγ modulates the expression of large gene arrays in adipose tissues, where it promotes adipogenesis, decreases free fatty acid (FFA) release, improves insulin sensitivity, and attenuates adipose inflammation (Fig. 2).

In humans, PPARα is predominantly expressed in tissues exhibiting high catabolic rates of fatty acids (adipose tissue, liver, heart, muscle, renal cortex), with lower levels in lung, placenta, intestine, pancreas, and skeletal muscle. PPARβ/δ is the most widely expressed isoform, with low levels found in almost all tissues examined. Unlike the other two PPAR isoforms, PPARγ is expressed the highest in adipose tissue, with lower levels in renal medulla, urinary bladder, skeletal muscle, liver, and heart (6, 62, 66). In addition, all PPAR subtypes are expressed in vasculature and various immune cells, where they exert their metabolic actions and modulate inflammatory processes.

The three PPAR isoforms also exhibit distinct ligand selectivity and biological activities. The divergent amino acid sequence in the ligand binding domain of the three subtypes is thought to be the molecular basis for ligand selectivity. Thus far a large group of exogenous compounds, including industrial chemicals such as herbicides and plasticizers, as well as synthetic pharmaceutical agents such as hypolididemic fibrates (e.g., fenofibrate and clofibrate) and antidiabetic TZDs, have been shown to bind to and activate PPARs (63). Endogenous fatty acids and their derivatives are capable of activating all three PPAR isoforms as well (93), although each PPAR shows some preference for specific fatty acids. Fatty acid derivatives, including 8-β-HETE, the arachidonic acid lipoxygenase metabolite LTβ4, and arachidonate monooxygenase (CYP2C) metabolite EETs, have been shown to potently activate PPARβ/δ (64), whereas naturally occurring prostacyclin and 15-deoxy-D12,14-prostaglandin J2 (15dPGJ2) have been identified as selective PPARβ/δ and PPARγ ligands, respectively. In addition, pathogenic-oxidized metabolites of linoleic acid, 9- and 13-hydroxy-octadecadienoic acids (9-HODE and 13-HODE), bind to PPARγ with weak affinity (127, 185). The demonstration that nutritional components and endogenous fatty acid metabolites are ligands for PPARs suggests that these receptors are under tight metabolic regulation and play an important role in body energy homeostasis. In fact, synthetic antidiabetic TZDs, including rosiglitazone and pioglitazone, are selective agonists for PPARγ and the hypolipidemic drugs of the fibrate class, including fenofibrate and clofibrate, are potent activators of PPARα. The development and clinical use of PPAR ligands have greatly advanced our understanding of the physiological and pathophysiological roles of PPARs and therapeutic implication of PPAR modulators in many metabolic diseases and related vascular complications.

**PPARα and MetS.** A large body of evidence demonstrates that PPARα plays an important role in the pathogenesis of MetS and may also constitute an attractive target for pharmacological intervention of MetS and its related cardiovascular complications.

PPARα has been found to play a critical role in lipid metabolism. The compelling evidence for a role of PPARα in lipid and energy homeostasis comes from gene-targeting experiments. PPARα-null mice exhibit higher serum levels of cholesterol and triglycerides (3). Moreover, these mice display extensive hepatic lipid accumulation and increased gonadal adipose storage and plasma FFA levels (107). In addition, the presence of severe hypoketonemia, hypoglycemia, and hypothermia in PPARα-deficient mice clearly supports a function of PPARα in metabolic regulation. Thus far, known target genes of PPARα are involved in almost all aspects of lipid metabo-
lism, including uptake, binding, and oxidation of fatty acids, lipoprotein assembly, and lipid transport (62). Transcription and protein levels of critical enzymes in fatty acid β-oxidation and ω-oxidation pathways, including acyl-CoA oxidase (AOX), carnitine palmityltransferase I (CPT-I), mitochondrial hydroxyethylglutaryl-CoA synthase (mHMG-CoAS), and cytochrome P-450 4A enzymes (CYP4As), are also under direct control of PPARα (62). Genes critical for VLDL lipolysis, lipoprotein lipase (LPL), apolipoprotein (apo) A-V (apoA-V), and apoCIII, are also target genes of PPARα. In addition, PPARα activation increases the synthesis of HDL and enhances reverse cholesterol transport through several PPARα-responsive genes such as apoA-I, apoA-II, LPL, adenosine triphosphate-binding cassette transporter-1 (ABC-1) and scavenger receptor class B type I (SR-BI), and CLA-1.

PPARα is an important regulator of insulin sensitivity. PPARα-deficient ob/ob mice develop severe pancreatic β-cell dysfunction with reduced mean islet area and decreased insulin secretion in response to glucose in vitro and in vivo (98). Mice with hemideficiency for both the LDL receptor (LDLR) and PPARα (LDLR+/−_PPARα+/−) show age- and gender-specific obesity and hyperinsulinemia (177). The role of PPARα in regulating insulin sensitivity is further supported by findings in nondiabetic and nonobese LDLR-null mice, in whom the PPARα agonist fenofibrate greatly reduced diet-induced obesity and improved insulin resistance (173). Similarly, in obese type 2 diabetic mice (db/db mice), PPARα activator markedly attenuated insulin resistance, glycemic control, and isletic β-cell dysfunction (1, 94, 143). The protective effect of PPARα is thought to be attributed to attenuated lipid toxicity in isletic β-cells. Indeed, PPARα-agonist treatment prevented fatty acid-induced impaired secretion of glucose-stimulated insulin, apoptosis, and triglyceride accumulation in primary cultured pancreatic islets (98). As well, PPARα agonist treatment in type 2 diabetic db/db mice improved pancreatic β-cell function and survival possibly by fibrolast growth factor 21 (FGF21)-dependent activation of ERK1/2 and Akt signaling pathways (194). Furthermore, recent findings demonstrated that the PPARα agonist fenofibrate not only ameliorated hyperinsulinemia but also prevented the development of diabetes in insulin-resistant obese OLETF rats (94). Thus PPARα could represent a promising target in the treatment and prevention of type 2 diabetes. In fact, PPARα agonists markedly attenuated glucose intolerance and improved insulin resistance in a lipotoxic diabetic patient (141) and in type 2 diabetic patients with hypertriglyceridemia (29). Collectively, these observations strongly support PPARα as a critical factor in insulin sensitivity regulation, and its activation may represent a valuable approach in prevention and treatment of type 2 diabetes.

PPARα may also contribute to the pathogenesis of obesity. Inactivation of the PPARα gene results in a late-onset obese phenotype (28), and treating PPARα-null mice with a high-fat diet led to a marked increase in body weight (89). As well, activation of PPARα reduced weight gain in rodents (177, 189) and insulin-resistant diabetic db/db mice treated with a dual PPARα and PPARγ activator, tesaglitazar, which exhibited glycemic control but without body weight gain, a common side effect of TZD (18).

PPARα has also been implicated in vascular inflammation and blood pressure regulation. The clinical features of MetS are associated with increased risk for cardiovascular disease. The beneficial effects of the fibrate class of PPARα agonists in the cardiovascular system mainly derive from their desirable action in lipid metabolism, and the anti-inflammatory effect of PPARα may play a role. In both vascular endothelial cells and vascular smooth muscle cells (VSMCs), where PPARα is constitutively expressed (119, 174), fibrate treatment inhibited the expression of many genes involved in vascular inflammation, oxidative stress, and cell growth and migration, mainly through blocking NF-κB, transforming growth factor (TGF)-β, Smad, and MAPK pathways (36, 92). Moreover, PPARα can suppress macrophage production of inflammatory cytokines (IL-1, IL-6, etc.) and reduce systemic inflammation via down-regulation of the acute-phase proteins fibrinogen C-reactive protein (CRP) and serum amyloid A in the liver (56). Recently, studies of ANG II-induced hypertension in rats revealed that PPARα agonists improved endothelial dysfunction, thereby significantly lowering blood pressure (34). Other potential mechanisms involved in the hypotensive effect of PPARα agonists may include enhanced transcription of arachidonate CYP450 4A enzymes (CYP4A14 knockout mice exhibit a phenotype of androgen-independent hypertension (75), whereas 4A10−/− mice show salt-sensitive hypertension (128). Collectively, PPARα could be a critical factor in regulating vascular biology and blood pressure.

Finally, although PPARα deficiency was associated with reduced atherosclerotic processes in apoE-null mice (186), PPARα activators may represent potential therapeutic agents in the treatment of atherosclerosis, a major cardiovascular complication associated with MetS. Treatment of apoE−/− mice and human apoAI transgenic apoE−/− mice with fibrates potently reduced atherosclerosis (42). Similarly, fibrate treatment of patients with dyslipidemia (53), type 2 diabetes (43), and MetS (157) resulted in much slower progression of atherosclerosis and significant risk reduction in cardiovascular events. Regarding the mechanism of the antiatherosclerotic effect of fibrate PPARα agonists, lipid-modulating, insulin-sensitizing, anti-inflammatory, and anti hypertensive actions are all believed to be involved in this highly desirable effect. These findings support the concept that fibrate PPARα agonists may confer protection against the cardiovascular complications of MetS.

Taken together, the results show that PPARα functions as a fatty acid sensor, contributes greatly to lipid metabolism and energy homeostasis, and participates in adipogenesis, blood pressure regulation, insulin sensitization, and immune-modulatory processes. From its known biological roles, PPARα is thought to be an important player in the pathogenesis of MetS. PPARα agonists were shown to be effective therapeutic agents for treating certain features of MetS, especially hyperlipidemia. Thus far, six major clinical trials have evaluated the safety and efficacy of fibrate on hyperlipidemia and the outcome of cardiovascular disease (7). Although fibrate clearly improved HDL-cholesterol levels and decreased triglyceride levels, mixed results were found in major outcomes such as mortality, chronic heart disease, and cardiovascular events. The limitation of fibrate as a single PPARα agonist may explain, in part, its lack of effect on prevention or as treatment of cardiovascular
PPAR\(\beta/\delta\) and MetS. Although PPAR\(\alpha\) and PPAR\(\gamma\) are attractive therapeutic targets for hyperlipidemia and type 2 diabetes, respectively, the physiological roles of PPAR\(\beta/\delta\) remain largely unknown, mainly because of a wide tissue distribution pattern and lack of a PPAR\(\beta/\delta\) ligand in current clinical use. The recent availability of global and tissue-specific PPAR\(\beta/\delta\) transgenic and gene-targeting mice has generated enormous valuable information, pointing to a role for PPAR\(\beta/\delta\) in insulin sensitivity regulation, adipogenesis, lipid metabolism, and the inflammatory response (85). Increasing evidence suggests that PPAR\(\beta/\delta\) may also represent a promising target for treating MetS and its associated cardiovascular complications.

PPAR\(\beta/\delta\) is important in adipose tissue metabolism. Gene manipulation studies revealed that a small number of global PPAR\(\beta/\delta\) gene-deficient mice who bypassed the lethal placental defect displayed a lean phenotype, with a significantly smaller amount of fat mass (9, 147). Paradoxically, a recent study involving transgenic mice with adipose tissue-selective overexpression of a constitutive active form of PPAR\(\beta/\delta\) (VP16-PPAR\(\beta/\delta\)) demonstrated reduced adiposity, with increased fatty acid oxidation and energy expenditure in fat tissues. In addition, these mice were protected against a high-fat diet-induced and genetically predisposed obesity (191). Similarly, the muscle-specific PPAR\(\beta/\delta\) transgenic mice displayed increased mitochondrial-rich, oxidative type-1 myofibers with enhanced oxidative enzymatic activities (115). Although the global deletion of the PPAR\(\beta/\delta\) gene and tissue-specific overexpression of the PPAR\(\beta/\delta\) gene result in similar metabolic phenotypes in adipose tissue is unknown, clearly, selective PPAR\(\beta/\delta\) agonists are effective in ameliorating diet-induced obesity and insulin resistance, concomitant with increased overall fatty acid oxidation and reduced tissue lipid content (182). Thus PPAR\(\beta/\delta\) may be a key regulator of fat catabolism and a potential therapeutic target for treating obesity and its associated metabolic disorders.

Evidence for PPAR\(\beta/\delta\) in regulating lipid metabolism is mainly provided by in vivo studies. PPAR\(\beta/\delta\)-null mice on a high-fat diet showed an increased rate of hepatic VLDL production, as well as lowered serum LPL activity, compared with wild-type controls, which indicates a clear role for PPAR\(\beta/\delta\) in regulating serum triglyceride levels in mice on a high-fat diet by modulating both VLDL production and LPL-mediated catabolism of VLDL triglycerides (171). In line with these observations, treatment of various animal models with selective PPAR\(\beta/\delta\) agonists, including GW0742 and L165041, yielded valuable data favoring PPAR\(\beta/\delta\) as a therapeutic target of dyslipidemia. Using a highly selective PPAR\(\beta/\delta\) agonist, L-165041, Leibowitz et al. (106) examined the effect of PPAR\(\beta/\delta\) activation on the plasma lipid profile in obese diabetic db/db mice and found that the PPAR\(\beta/\delta\) agonist significantly increased the HDL-cholesterol level, possibly via decreasing LPL activity in white adipose tissue. On treating insulin-resistant middle-aged obese rhesus monkeys with another PPAR\(\beta/\delta\) agonist, GW501516 (\(K_i = 1.1 \pm 0.1\) nM), Oliver et al. (136) provided confirmatory evidence that such treatment significantly increased the HDL-cholesterol level and accumulation of large-sized HDL particles, markedly reduced triglyceride and LDL-cholesterol levels, and improved fasting insulin levels. These findings firmly demonstrate a potential therapeutic role for PPAR\(\beta/\delta\) in improving serum lipid levels in MetS.

The PPAR\(\beta/\delta\) receptor also plays a key role in insulin resistance and glucose metabolism. Recently, Lee et al. (104) reported that PPAR\(\beta/\delta\) knockout mice were metabolically less active and glucose intolerant, whereas receptor activation in db/db mice improved insulin sensitivity as a result of suppressed hepatic glucose output, increased glucose disposal, and inhibited FFA release from adipocytes. The selective PPAR\(\beta/\delta\) agonist GW501516 dose dependently lowered plasma insulin levels without affecting weight gain in a primate model of insulin resistance (136). In agreement with this finding, GW501516 treatment of ob/ob mice, a model of MetS, also markedly attenuated glucose tolerance and improved insulin resistance (182). Although the underlying mechanisms are unclear, the actions of PPAR\(\beta/\delta\) are believed to contribute to the beneficial metabolic effects of PPAR\(\beta/\delta\) agonists in insulin resistance, possibly through upregulation of genes involved in fatty acid transport, \(\beta\)-oxidation, mitochondrial respiration, and hepatic gluconeogenesis (40, 104, 115, 182) in the skeletal muscle, liver, and adipose, three major targets for insulin action (60).

Finally, PPAR\(\beta/\delta\) exhibits potent anti-inflammatory properties, but its role in atherosclerosis is being debated. Macrophages with PPAR\(\beta/\delta\) deactivation (PPAR\(\beta/\delta\)-null) or activation both show decreased expression of inflammatory factors, including monocyte chemotactic protein 1 (MCP-1) and IL-1\(\beta\) (103). In addition, PPAR\(\beta/\delta\) agonists suppress the gene expression of TNF-\(\alpha\)-induced MCP-1 and VCAM-1 in cultured endothelial cells (152). The molecular mechanism(s) for the anti-inflammatory action by both PPAR\(\beta/\delta\) inactivation and activation are not completely clear. The recruitment of different coregulators for the PPAR\(\beta/\delta\)-ligand complex or differential modification of coregulators may play a role in switching the transcriptional regulation by PPAR\(\beta/\delta\). Studies of mouse atherosclerotic models also led to inconsistent conclusions. Graham et al. (58) reported that the PPAR\(\beta/\delta\) ligand is effective in reducing atherosclerosis in LDLR-knockout mice by inhibiting inflammation (58), whereas Li et al. (109) failed to show any improvement with PPAR\(\beta/\delta\) agonists in the same model. A recent study involving a PPAR\(\beta/\delta\) knockout transplantation strategy revealed a marked reduction in atherosclerotic lesions compared with use of PPAR\(\beta/\delta\)-null bone marrow transplantation in \(\gamma\)-irradiated LDLR-knockout mice fed a high-fat diet, which suggests that PPAR\(\beta/\delta\) inactivation in macrophages or vascular progenitor cells is beneficial (103). Although genetic and pharmacological approaches demonstrated that PPAR\(\beta/\delta\) is not implicated in cholesterol metabolism, it has been found to mediate cholesterol efflux via increasing the expression of the reverse cholesterol transporter ATP-binding cassette A1 (ABCA1) from different cell types (136). Additionally, PPAR\(\beta/\delta\) can serve as a cellular VLDL sensor and mediate VLDL triglyceride-driven transcription events in macrophages (22). Activation of PPAR\(\beta/\delta\) by fatty acids from VLDL-triglyceride particles leads to triglyceride accumulation and an induced adipecyte phenotype, which can be blocked by disruption of PPAR\(\beta/\delta\) gene expression (104). Collectively, these observations suggest that PPAR\(\beta/\delta\) may thus attenuate inflammation and slow the progression of ath-
erosclerosis. Nevertheless, whether PPAR\(\beta/\delta\) agonists are beneficial in atherosclerosis remains unclear.

Taken together, emerging evidence suggests that PPAR\(\beta/\delta\) is a pivotal factor in metabolic control. PPAR\(\beta/\delta\) may play a role in the pathogenesis of MetS. Pharmacological targeting may represent a useful approach for treating dyslipidemia, obesity, insulin resistance, and, possibly, atherosclerosis (85, 180). Unlike PPAR\(\alpha\) and PPAR\(\gamma\), little is known about the potential safety issues that could be involved in the use of PPAR\(\beta/\delta\) ligands. Increasing evidence suggests that PPAR\(\beta/\delta\) ligands might be carcinogetic (156).

**PPAR\(\gamma\) and MetS.** In the past decade, enormous research efforts have identified PPAR\(\gamma\) as a central player in MetS. PPAR\(\gamma\) has been implicated in almost all aspects of metabolic disorders, including obesity, insulin resistance, dyslipidemia, inflammation, and hypertension. The identification of the synthetic TZDs as potent PPAR\(\gamma\) agonists and use of these compounds in treating insulin resistance and type 2 diabetes greatly facilitate our understanding of PPAR\(\gamma\) function. In addition to its role in insulin resistance, PPAR\(\gamma\) has now become an attractive therapeutic target in the treatment of obesity, hypertension, dyslipidemia, and atherosclerosis (69).

As a central feature of MetS (125), insulin resistance is considered an early stage of type 2 diabetes. A crucial initial indication of the importance of PPAR\(\gamma\) in insulin resistance stems from a finding that PPAR\(\gamma\) is the molecular target of the TZD insulin-sensitizing agents, two of which (rosiglitazone and pioglitazone) have been widely used as antidiabetic drugs (105). Extensive human genetic studies further shed light on a critical role of PPAR\(\gamma\) in insulin sensitivity regulation (68). Loss-of-function mutations in the ligand-binding domain of human PPAR\(\gamma\) resulted in PPAR\(\gamma\)-ligand resistance syndrome, with severe insulin resistance, partial lipodystrophy, diabetes, hypertension, and dyslipidemia, in part due to skeletal muscle and liver steatosis (10, 72, 168). The targeting tissues responsible for the regulatory effect of PPAR\(\gamma\) on insulin sensitivity appear to be complicated and remain incompletely understood.

TZD PPAR\(\gamma\) agonists increase the sensitivity of the liver to insulin-mediated suppression of glucose production and enhance glucose utilization of the skeletal muscle (56, 214). Adipose tissue may also be an important target of TZD action, since PPAR\(\gamma\) activation increases glucose uptake and results in profound changes in adipokines, including suppression of insulin-insensitizing TNF\(\alpha\), IL-6, and resistin and induction of insulin-sensitizing adiponectin (27, 45, 120, 163, 170, 175, 200, 202). Paradoxically, insulin resistance develops in mice with selective ablation of PPAR\(\gamma\) in fat tissue, which responds to TZD treatment (16, 41), and in macrophages, which are responsive only in part to TZD treatment (74, 132), thus revealing an essential role of PPAR\(\gamma\) in adipocytes and macrophages in maintaining whole-body insulin action and mediating the antidiabetic actions of TZDs. To date, various mouse models of PPAR\(\gamma\) deficiency, including global (41) and adipose-, skeletal muscle- and liver-specific PPAR\(\gamma\)-null lines, have been generated to dissect the function of PPAR\(\gamma\) in different tissues (55, 73, 82). These murine lines have provided valuable insights into the function of PPAR\(\gamma\) but also reveal a picture of complexity. The study of these models has confirmed a key role of PPAR\(\gamma\) in regulating insulin sensitivity, with the molecular mechanisms incompletely understood (41, 59). In addition to adipocyte-derived adipokines, the AMPK signaling pathway may play a critical role in mediating the insulin-sensitizing action of TZDs. TZDs can activate AMPK (102), which, in turn, increases insulin sensitivity (48). Additionally, TZD-induced adiponectin may sensitize the insulin action via an AMPK-dependent pathway in adipose tissue, skeletal muscle, and liver (130, 199). Thus PPAR\(\gamma\) is a central player in body insulin sensitivity. Multiple mechanisms are involved in the TZD-mediated insulin-sensitizing action in several key tissues, including the liver, skeletal muscle, and adipose tissue. Mechanistic information obtained from additional in vitro and in vivo studies will contribute further insights into PPAR\(\gamma\) action and its clinical implications.

The abnormality in PPAR\(\gamma\) is directly linked to obesity. Although PPAR\(\gamma\) is found in various tissues, it is highly expressed in adipose tissues, where it is critical in adipocyte differentiation or adipogenesis (114). In vivo studies further supported a key role for PPAR\(\gamma\) in fat formation. PPAR\(\gamma\)-null mice completely lack adipose tissues, but TZD treatment markedly increased body weight (41, 59, 153). A role for PPAR\(\gamma\) in adiposity is also strongly supported by results from the study of PPAR\(\gamma\) mutation and polymorphisms in humans. For instance, in vitro analysis revealed an alanine substitution at position 12 proline in the extra NH\(_2\)-terminal residues of adipose tissue-restricted PPAR\(\gamma\)-2, leading to a lower affinity for PPRE and decreased transactivation. Some individuals with this alanine/proline substitution showed low body mass and decreased risk for type 2 diabetes (31, 68). However, patients with glutamine substitution at position 115 proline, which leads to increased PPAR\(\gamma\) activity, exhibited severe obesity (151). PPAR\(\gamma\) controls the expression of an array of genes involved in lipogenesis and triglyceride storage, including adipocyte fatty acid binding protein (aP2, or AFABP), phosphoenolpyruvate carboxykinase, acyl-CoA synthase, FATP, fatty acid translocase, and LPL (62, 211). In vitro studies clearly demonstrated that activation of PPAR\(\gamma\) by TZDs or retroviral expression of PPAR\(\gamma\) stimulates adipogenesis, whereas inhibition of PPAR\(\gamma\) by a dominant-negative PPAR\(\gamma\) mutant completely blocked the effect (14, 70). In addition, TZD treatment resulted in redistribution of body fat, with significantly increased subcutaneous adipose deposits, and patients treated with TZD showed increased body weight (215). Collectively, these data demonstrate that PPAR\(\gamma\) plays a pivotal role in the regulation of adipocyte function and the pathogenesis of obesity.

PPAR\(\gamma\) is an important regulator in lipid homeostasis. Genetic studies have provided important insights into the role of PPAR\(\gamma\) in lipid metabolism. Loss-of-function mutations in PPAR\(\gamma\) lead to an elevated triglycerides level and reduced HDL-cholesterol level in humans (10, 164). Similarly, PPAR\(\gamma\) gene deficiency results in elevated levels of triglycerides (82) and plasma nonesterified fatty acids (NEFAs) (41). In clinical practice, the TZD PPAR\(\gamma\) activators troglitazone and pioglitazone improved dyslipidemia by elevating the HDL-cholesterol level and lowering the triglyceride level (4, 50, 95, 97, 124). The TZDs rosiglitazone and pioglitazone were effective in reducing the serum level of FFAs (121, 124), which may contribute to their ability to improve insulin resistance. Although TZDs caused only a slight increase in the LDL-cholesterol level, they increased the level of relatively large and less atherogenic, buoyant LDL particles and decreased the number of small but more atherogenic and dense particles (52,
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179). Furthermore, both rosiglitazone and pioglitazone are effective and well tolerated when used in combination with statins (52, 91), which likely add additional beneficial effects for dyslipidemia in patients with MetS.

PPARγ is involved in blood pressure regulation. To date, whether PPARγ is hypertensive or hypotensive is being debated (192). Genetic studies showed mice with global PPARγ gene ablation with low blood pressure (41), which is consistent with a finding that PPARγ agonist stimulates renin gene expression (184). These observations point to a hypertensive role for PPARγ in blood pressure regulation. However, PPARγ activation was also found to confer beneficial effects for hypertension in both animal and human studies (8, 80, 133, 159, 204). In animal models of insulin resistance or hypertension or both, TZD treatment lowered blood pressure or protected against the development of hypertension (15, 38, 190, 204). In MetS patients (the PROactive Trial), TZD treatment was associated with reduced blood pressure, which may subsequently contribute to a significant decrease in cardiovascular mortality (39). Although the hypotensive effect of TZDs is generally attributed to their ability to enhance insulin sensitivity (61, 178, 188, 190, 205), the direct action of PPARγ agonists on vessels could also play a role. PPARγ is found to be expressed in both endothelial cells and VSMCs (78, 100, 117, 118, 162). Studies of noninsulin-resistant hypertensive animals, including 1K/1C and ANG II-induced hypertension and human renin/angiotensinogen transgenic mice further support that TZDs can exert their antihypertensive effects via direct vascular action (35, 158, 210). To date, the underlying mechanisms are still under investigation. PPARγ activation may regulate blood pressure via modulating endothelial vasoactive factors such as endothelin-1, prostacyclin, and nitric oxide (NO). PPARγ may also directly reduce VSMC tone through downregulating ANG II receptor 1 (AT1-R) (181). In addition, attenuation of sympathetic overactivity and renal action may be involved in the hypotensive effect of TZDs (161). Interestingly, some of angiotensin-receptor blocking (ARB) agents, including telmisartan, can activate PPARγ, which implies that ARB agents could treat both the hemodynamic and metabolic aberrations seen in MetS subjects with insulin resistance, glucose intolerance, and hypertension (187). Collectively, results indicate that PPARγ activation is generally thought to modestly lower blood pressure via a mechanism involving a delicate balance between the effect of PPARγ agonists on the renin-angiotensin system and other vasoactive substances.

Finally, PPARγ has been implicated in almost all the pathological processes contributing to atherosclerosis, including endothelial dysfunction, leukocyte chemotaxis, foam cell formation, and plaque evolution, destabilization, and rupture (76). LDLR-null mice transplanted with PPARγ-null bone marrow exhibited a worsened atherosclerotic phenotype (21). In agreement with this finding, a large body of evidence indicates that TZDs exhibit antiatherogenic effects independently of their antidiabetic and lipid-lowering properties by modulating inflammatory processes (13, 26, 110, 122). PPARγ agonists may indirectly suppress the systemic production of a proinflammatory milieu mainly via inhibiting TNF-α, PAI-1, and IL-6 expression in adipose tissue (30, 32). Additionally, PPARγ has long been known to have anti-inflammatory effects on monocytes. PPARγ activation can reduce the production of cytokines (TNF-α, IL-1, IL-6) (81), probably through inhibiting the activity of proinflammatory transcription factors such as NF-κB, AP-1, and STAT (134). TZDs also limit vascular inflammation by reducing hepatic CRP production and subsequently alleviating CRP-mediated upregulation of proinflammatory ICAM, VCAM, and MCP-1 in vascular cells (13). With respect to lipid metabolism, PPARγ activation increases cholesterol efflux from macrophages via upregulation of the ABAC1 gene, as a consequence of activating the PPARγ-liver X receptor (LXR)-ABAC1 pathway (21, 25). Therefore, although PPARγ may promote cholesterol influx as a result of increased CD36 expression, the action of PPARγ on macrophages seems to be beneficial via a dominant effect on the efflux of lipids, thereby blocking foam cell formation. PPARγ also reduces VSMC proliferation, increases monocyte apoptosis, and suppresses metalloproteinase-9 expression in atherotic plaques (24, 100, 101, 118). From these findings, TZD PPARγ agonists clearly constitute useful therapeutic agents in MetS and its cardiovascular complications.

Although the TZD class of PPARγ agonists is generally well tolerated, their administration is associated with a number of safety issues. The adverse effects can be categorized as either unique to individual TZDs or common to the class. Hepatotoxicity, a unique side effect of the first-generation TZD troglitazone, is less commonly seen on treatment with rosiglitazone and pioglitazone. Class adverse effects include body weight gain, hemodilution, peripheral edema, mild anemia, and, possibly, increased risk of congestive heart failure, which may limit clinical use of the drugs (156, 213).

PPARs and CKD Associated With MetS

The increasing prevalence of MetS, particularly obesity and diabetes mellitus, in most industrialized countries is reaching epidemic proportions and requires intense studies and interventions. MetS with insulin resistance as a hallmark is often the precursor of diabetes mellitus and is associated with increased risk of cardiovascular complications. Recently, a growing body of evidence suggests that MetS may also be associated with a high risk for CKD (113). A large population-based study, The Third National Health Nutrition and Examination Survey (NHANES), established a close relationship between insulin resistance and CKD, including reduced glomerular filtration rate (<60 ml·min⁻¹·1.73 m⁻²) and microalbuminuria (23). Hypertension has long been established as an important cause of CKD, whereas the association between obesity and renal dysfunction was only recently clarified (83). In addition, renal-insufficient patients share similar cardiovascular risk factors with patients with classic MetS and frequently develop insulin resistance, dyslipidemia, and hypertension (49, 87, 99). Therefore, treatment of both MetS and CKD should have a great impact on cardiovascular mortality with both diseases.

As discussed above, all three PPAR isoforms have been identified as therapeutic targets in treatment of MetS. Therapeutic approaches based on modulating PPAR activity have also been shown to attenuate or even prevent CKD. The following presents recent insights into the therapeutic implications of PPAR agonists in CKD associated with insulin-resistant type 2 diabetes.
Intrarenal localization of PPARα, PPARβ/δ, and PPARγ. The kidney expresses all three types of PPARs. PPARα is highly abundant in the proximal tubules and medullary thick ascending limbs, with much lower levels in glomerular mesangial cells (66). Renal PPARβ/δ appears to be expressed in a diffuse pattern and has been found in both the cortex and medulla, including in glomerular mesangial cells, medullary interstitial cells, and stromal cells (12, 66). PPARγ is predominantly expressed in the distal medullary collecting ducts and, to a lesser extent, in glomeruli and renal microvasculature (66, 67). Low but significant expression of PPARγ is also present in many other nephron segments such as the proximal tubules (64). In addition, constitutive expression of PPARγ has been reported in cultured glomerular mesangial cells, podocytes, proximal epithelial cells, and epithelial cells of collecting ducts (211). Together, these findings point to the diverse roles of the PPAR family in regulating renal physiology and pathophysiology.

PPARα and diabetic nephropathy. PPARα with high expression in the proximal tubules plays an important role in the metabolic control of renal energy homeostasis (148). PPARα controls a set of genes essential for fatty acid β-oxidation in the renal cortex and contributes to an appropriate adaptive response to dietary lipids by the kidney. In support of this, the kidney response to starvation in PPARα-null mice was blunted (176). These observations collectively suggest that PPARα may participate in certain renal pathophysiological settings associated with dysregulation of energy homeostasis such as diabetic nephropathy. However, whether PPARα activation is beneficial in diabetic nephropathy is uncertain; an early study involving a transgenic mouse line with cardiac overexpression of PPARα reported an adverse effect on cardiomyopathy (47), and a recent report demonstrated a renoprotective effect of PPARα deficiency in elderly mice fed a high-fat diet (17). This finding raises a serious concern about the safety of oral fibrate treatment in patients with diabetic nephropathy in that a marked increase in PPARα gene expression has been documented in the diabetic kidney (123). However, several recent clinical studies provided clear-cut lines of evidence that the fibrate class of PPARα agonists confer a renoprotective effect in patients with type 2 diabetes (54, 90). For example, in normotensive nonsulin-dependent diabetic patients, treatment with the PPARα activator gemfibrozil not only alleviated dyslipidemia but also attenuated albuminuria (172).

The underlying mechanisms by which PPARα agonists attenuate the features of diabetic nephropathy remain elusive. By using the db/db mouse as a model of type 2 diabetes, Park et al. (143) examined the effect of fenofibrate treatment on insulin resistance, glycemic control, and renal pathology. A 2-mo treatment significantly attenuated insulin resistance and hyperglycemia and markedly reduced albuminuria and renal fibrosis (143). In contrast, PPARα gene deficiency was found to be associated with exacerbated diabetic nephropathy, with more severe albuminuria and worsened renal injury (142). The renal-protective effect of PPARα agonists is apparently multifactorial. In addition to systemically attenuating insulin resistance and dyslipidemia, the agonists may have a direct beneficial action on the kidney. One possible mechanism may involve a TGF-β signaling pathway. PPARα activators may exert direct effects on mesangial cells, where PPARα activation was found to block oxidant-stress-induced TGF-β1 expression, thereby attenuating glomerular matrix production (195). This finding was further supported by another recent study demonstrating that fenofibrate downregulated TGF-β1 and TGF-β signaling receptor II (TβRII) and decreased collagen IV deposition in diabetic glomeruli (Park CW, unpublished observations). In addition, starved PPARα-null mice showed increased urine albumin excretion and albumin accumulation in proximal tubules (84). This finding suggests that PPARα activation may promote albumin reabsorption and degradation in this nephron segment, which may then mediate the albuminuria-reducing effect of PPARα agonists in diabetic nephropathy. Finally, PPARα agonists increased both LXRα and ABCA1 gene expression and enhanced apoA1-mediated cholesterol efflux from lipid-loaded mesangial cells, thereby attenuating renal lipotoxicity (155). Thus PPARα is important in the pathogenesis of diabetic nephropathy and may be a promising therapeutic target for treating diabetic renal complications.

PPARβ/δ and diabetic nephropathy. Although PPARβ/δ is known as the ubiquitously expressed PPAR isoform in the kidney (66, 71), its role in the kidney is just being elucidated. PPARβ/δ may play an important role in renal metabolic adaptation to fasting and refeeding (62), which suggests its involvement in metabolic kidney diseases such as diabetic nephropathy. In fact, in Akita and OVE26 mice with type 1 diabetes, the renal expression of PPARβ/δ is greatly suppressed, which may contribute to renal lipotoxicity because of reduced fatty acid oxidation (149). Consistent with this hypothesis, treatment of mesangial cells with IGF-1, a cytokine upregulated in the diabetic kidney (19), enhanced triglyceride accumulation, possibly via increasing VLDL receptor expression resulting from PPARβ/δ suppression (12). These findings clearly point to reduced renal PPARβ/δ expression possibly representing an underlying mechanism involved in diabetic kidney injury. Abundant and active PPARβ/δ was observed in cultured renal medullary interstitial cells. Overexpression of PPARβ/δ provides protection against hypertonicity-induced cell death in cultured medullary interstitial cells, which suggests that PPARβ/δ is an important survival factor in the kidney (71). In agreement with this finding, a recent study by Letavernier et al. (108) showed that PPARβ/δ can provide strong protection against ischemia-induced renal injury as a result of its combined action on cell survival and cytoskeletal reorganization. Collectively, PPARβ/δ agonists may be considered a novel means of conferring renal protection in diabetic nephropathy and other kidney diseases.

PPARγ and diabetic nephropathy. Since the introduction of TZD insulin sensitizers in diabetic clinical treatment, the role of PPARγ in the kidney and the potential of PPARγ agonists as therapy in diabetic nephropathy have been extensively investigated. Most currently available clinical studies demonstrate a renoprotective effect of PPARγ agonists in type 2 diabetic patients with or without hypertension, as indicated by reduced albuminuria (77, 160, 203, 213). Importantly, compared with insulin and other oral hypoglycemic agents, including metformin, glyburide, and glibenclamide, all tested TZD PPARγ agonists (troglitazone, rosiglitazone, and pioglitazone) produce similar glycemic control but appear to provide superior renal protection in humans with type 2 diabetes (79, 129, 135, 196). Similarly, a beneficial effect on urine albumin excretion and/or renal fibrosis in animal models of insulin resistance, type 2 diabetes, and hypertension has been consis-
tently reported for glitazone, rosiglitazone, and pioglitazone (77). In parallel with findings in type 2 diabetic patients, TZD has been shown to provide superior renal protection vs. angiotensin-converting enzyme inhibition against renal injury in type 2 diabetic rats (11). These positive effects suggest that TZD may be a therapeutic drug for MetS or obesity-related CKD. Although PPARγ agonists have been demonstrated to be insulin sensitizers and repeatedly shown to reduce albuminuria and provide renal protection, TZD treatment results in weight gain and fluid retention (65). Thus a large, randomized-perspective clinical trial is needed to determine whether TZD treatment is beneficial and to examine the consequences of its long-term side effect(s).

Growing evidence supports TZDs with several beneficial effects on the kidney beyond their effects on glycemic control and hypertension. This suggestion is supported by results of several in vivo studies showing TZD PPARγ agonists effective in attenuating diabetic nephropathy in type 1 diabetes (131, 134). The direct actions of TZDs on the kidney are also supported by many results of in vitro studies of freshly isolated glomeruli (67) and cultured renal cells, including mesangial cells, podocytes, proximal tubule cells, collecting duct cells, and renal fibroblasts (67, 211). As described in the preceding sections, multiple renal cell types exhibit endogenous PPARγ activity and represent the direct targets of PPARγ agonist action within the kidney. In addition to the medullary collecting duct, where PPARγ mediates TZD-induced fluid retention (65, 209), renal glomeruli and proximal tubules are thought to be major sites of PPARγ action (211). The benefits of PPARγ agonists in mesangial cells include 1) inhibition of high glucose- or TGF-β-induced extracellular matrix biosynthesis (154, 212); 2) reduction of TGF-β1 transcription induced by high glucose (193); 3) arrest of cell growth and blockade of mesangial cell dedifferentiation (5, 67, 131); 4) inhibition of platelet-derived growth factor (PDGF)- and VEGF-induced mesangial growth (57, 137); 5) suppression of proinflammatory cytokine expression in mesangial cells (198); 6) attenuation of lipotoxicity through activation of the LXRα-ABCA1 pathway (197); 7) inhibition of iNOS, COX-2, and PAI-1 expression (20, 165, 206); and 8) induced expression of antifibrotic hepatectoy growth factor (112). In addition, glomerular podocytes and endothelial cells represent additional targets for PPARγ agonists in the kidney (86). Functional PPARγ expression has been previously reported in glomerular endothelial cells and podocytes (67, 116). In recent studies, Yang (201) and Kanjanabuch et al. (86) found that pioglitazone protected against puromycin aminonucleoside nephropathy via activation of podocyte PPARγ and restoration of podocyte function. Moreover, several lines of evidence have shown low but significant levels of PPARγ in cultured proximal tubular cells (111, 139). Activation of PPARγ by non-TZD L-805645 reduces proximal tubular cell proliferation and high-glucose-induced TGF-β1 and MCP-1 expression in HK-2 cells (139). Pioglitazone is also able to exert antifibrotic effects in these cells under high-glucose conditions by attenuating the increase in AP-1 and TGF-β1 and the downstream production of fibrinectin (138, 140). In accordance with these findings, an antifibrotic and anti-inflammatory effect of PPARγ agonists was observed in an opossum kidney model of proximal tubular cells challenged with LDL (207). Similarly, endogenous PPARγ is present in human kidney fibroblasts, where its activation results in cell growth arrest and extracellular matrix reduction (208). Collectively, these results suggest that PPARγ activation exerts antiproliferative, antifibrotic, and anti-inflammatory actions in many renal cells, thereby ameliorating the course of progressive glomerular and tubulointerstitial fibrosis in hyperglycemic states.

In summary, PPARγ agonists can improve urine albumin excretion and slow the progression of chronic renal disease in both animals and humans. Multiple systemic and local mechanisms, including improved glycemic control and hypertension, as well as direct actions on glomeruli and tubulointerstitium, mediate this renoprotective role of TZDs (Fig. 3). With these desirable renal effects, PPARγ is a promising target for treating glomerular fibrotic diseases, especially diabetic nephropathy.

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Fig. 3. Summary of the therapeutic actions of three PPAR isoforms in diabetic nephropathy. Both systemic actions and direct renal effects are involved in the renoprotective effect of PPAR ligands. BP, blood pressure; iNOS, inducible endothelial nitric oxide synthase; COX-2, cyclooxygenase-2; TGF, transforming growth factor; PAI-1, plasminogen activator inhibitor-1.
Conclusions and Perspectives

The global epidemic of MetS, especially insulin resistance, type 2 diabetes, and obesity, has led to a rapid increase in the prevalence of chronic renal disease. Although type 2 diabetes-associated diabetic nephropathy remains the number-one cause of chronic renal disease, other features of the syndrome, such as obesity and dyslipidemia, have recently been considered important contributors to chronic renal insufficiency. However, patients with chronic renal disease may also represent a unique population with a high risk for MetS and cardiovascular disorders. Therefore, new strategies for prevention and treatment of both MetS and CKD are urgently needed to reduce cardiovascular mortality, a common serious consequence of the two diseases.

During the past decade, considerable evidence has indicated that all three PPAR subtypes, PPARα, PPARβ/δ, and PPARγ, are involved in the pathogenesis of MetS, and their ligands may have great therapeutic potential in treating this cluster of metabolic diseases. Some PPAR agonists are also effective in lowering urine albumin excretion and attenuating the progressive loss of renal function in diabetic and nondiabetic subjects. Both systemic metabolic changes and local direct action at the kidney level are believed to be the underlying mechanisms for the renoprotective effect of such agonists (Fig. 3). However, further studies are clearly needed to detail the renoprotective mechanisms and establish the therapeutic potential and adverse effects of PPAR agonists in patients with MetS and renal function damage.

All three PPAR isotypes exert complementary physiological functions at distinct and common sites of action and provide potential therapeutic benefit in type 2 diabetes and its cardiovascular consequences. Thus one might expect the combination of an available PPARα agonist with a TZD and ligands capable of activating two or three PPAR subtypes to have a good therapeutic but reduced side effect profile (2). In fact, a recent clinical study showed that the addition of fenofibrate to rosiglitazone for patients with type 2 diabetes and poor metabolic control was well tolerated and significantly decreased LDL-cholesterol and triglyceride levels and markedly increased the HDL-cholesterol level (167). However, although currently available dual agonists for PPARα and PPARγ, namely, glitazars, including muraglitazar and tesaglitazar, have shown promise in lowering glucose and improving the lipid profile in type 2 diabetic patients with atherogenic dyslipidemia, they have presented problems at a late stage of the clinical trials because of serious cardiorenal side effects (183). With regard to the effect on diabetic nephropathy, in one of our studies, tesaglitazar was found to significantly reduce albuminuria and renal fibrosis without body weight gain in db/db mice (18). Importantly, therapy with a well-known lipid-lowering fibric acid derivative, bezafibrate, which represents a weak panagonist for all three PPARs, has considerable benefit for dyslipidemia and insulin resistance, significantly lowering the incidence of cardiovascular events and onset of type 2 diabetes in patients with MetS, and it has a good safety profile (183). Recently, research efforts have been directed at developing selective PPAR modulators (SPPARMs) with pharmacological efficacy and minimal adverse effects; examples include megilidase, FMOC-leu, nTZDpa, SPPPARM12, and the T131 molecule (156, 169). Future generations of PPAR modulators should retain high effectiveness but have fewer side effects for patients with MetS and associated chronic renal disease.

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