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PPAR γ REGULATION IN HYPERTENSION AND METABOLIC SYNDROME

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Abstract

Dysregulation of Peroxisome Proliferator Activated Receptor γ (PPAR γ) activity leads to significant alterations in cardiovascular and metabolic regulation. This is most keenly observed by the metabolic syndrome-like phenotypes exhibited by patients carrying mutations in PPAR γ . We will summarize recent findings regarding mechanisms of PPAR γ regulation in the cardiovascular and nervous system focusing largely on PPAR γ in smooth muscle, endothelium and brain. Canonically PPAR γ exerts its effects by regulating the expression of target genes in these cells, and we will discuss mechanisms by which PPAR γ targets in the vasculature regulate cardiovascular function. We will also discuss emerging evidence that PPAR γ in the brain is a mediator of appetite and obesity. Finally, we will briefly review how novel PPAR γ activators control post-translational modifications of PPAR γ and their prospects to offer new therapeutic options for treatment of metabolic diseases without the adverse side effects of thiazolidinediones which strongly activate transcriptional activity of PPAR γ .

Keywords

PPAR γ ; ubiquitin ligase; vascular function; brain; posttranslational modifications

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Conflict of Interest

The authors declare no conflicts of interest.

Introduction

Metabolic syndrome (MetS) is a disorder of energy balance that has reached pandemic proportions as it now affects a quarter of the world's population. MetS is characterized by several main factors including obesity, dyslipidemia, hypertension, insulin resistance, increased systemic inflammation and hypercoagulability. Once diagnosed with MetS, patients are at a significantly higher risk for development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases as early as 5 years after diagnosis. Compared to healthy individuals, MetS diagnosis imposes an increased risk of stroke as well as myocardial infarction, even in the absence of a history of cardiac problems. Today, children and adolescents present with health problems, which were previously observed only in adults, and thus Pediatricians routinely see patients with high blood pressure (BP), T2DM and increased blood cholesterol.

In the past several decades, the Peroxisome Proliferator-Activated Receptors (PPARs) class of nuclear receptor superfamily transcription factors have gained significant prominence as important regulators of nutrient sensing as well as lipid and glucose metabolism. The PPARs consist of three isotypes: PPAR α (NR1C1), PPAR δ or β (NR1C2) and PPAR γ (NR1C3). Although all three are strongly implicated as therapeutic targets in MetS [1, 2], we will specifically focus on PPAR γ as a key modulator of processes related to vascular and metabolic homeostasis (Figure).

The importance of PPAR γ in the maintenance of normal BP and systemic metabolism is corroborated by the MetS-like phenotypes (hypertension [3], insulin resistance [4], lipodystrophy [3, 5], and dyslipidemia [6]) that occur in patients carrying mutations in the *PPARG* gene. The first heterozygous loss-of-function mutations (P467L or V290M) in the ligand-binding domain of PPAR γ were reported in 1999 [4]. The affected subjects exhibited early onset of severe hypertension, insulin resistance in the context of T2DM diagnosis, and dyslipidemia, but generally normal body weight [4, 7]. In contrast, a gain of function mutation (P115Q) in PPAR γ has been reported to lead to severe obesity [8]. Contrary to the effects of PPAR γ mutations, the thiazolidinediones (TZDs), synthetic activators of PPAR γ , are potent insulin sensitizers in the treatment of T2DM [9], have been shown to improve serum lipid profiles in T2DM patients [10], and to decrease BP [11]. Clearly understanding the mechanisms of how modulation of PPAR γ activity can lead to such drastic shifts in metabolic outcomes can result in development of targeted therapies with enhanced impact.

Role of PPAR γ in Atherogenesis

TZDs have been shown to exert protective effects in the development of atherosclerotic disease [12–14]. Experimental evidence from animal models shows that TZDs inhibit the formation of atherosclerotic lesions [15, 16]. Current data suggests that the beneficial effects are not simply a consequence of improved insulin sensitivity, but a direct result of PPAR γ activation. PPAR γ is expressed in monocytes/macrophages, T-lymphocytes, vascular endothelial cells (EC), and smooth muscle cells (SMC), all of which are critical components of atherosclerotic lesions. Thus, studies have been designed to assess which cell type is the target of the beneficial effects of TZD on lesion formation. In human carotid atherosclerotic

plaques, PPAR γ activation drives the differentiation of anti-inflammatory M2 instead of pro-atherogenic M1 macrophages, resulting in reduced release of inflammatory cytokines including tumor necrosis factor α (TNF- α) and monocyte chemoattractant protein-1 (MCP-1) [17]. In mice, macrophage-specific deletion of PPAR γ disrupts the activation of M2 cells [18]. Activation of PPAR γ in macrophages [19] and T cells [20] inhibits the inflammatory effects of transcription factors such as nuclear factor κ B (NF- κ B) and activator protein 1 (AP1). Indeed, NF- κ B-induced proinflammatory signals drive initiation, progression and development of atherosclerotic lesions [21, 22].

In addition to the effects of PPAR γ on inflammatory cells, which can migrate to an atherosclerotic lesion, evidence suggests that PPAR γ activity in both EC and SMC can effect lesion formation. When challenged with a high-cholesterol diet, LDL receptor (LDLR) knockout mice with EC-specific deletion of PPAR γ (EC- PPAR $\gamma^{-/-}$ mice) demonstrate significantly accelerated atherosclerotic lesion formation compared to either littermate controls or LDLR knockout mice with macrophage-specific PPAR γ disruption [23]. Macrophage infiltration and pro-inflammatory gene expression are increased in aortic lesions from EC- PPAR $\gamma^{-/-}$ deficient mice on LDLR knockout background. Similarly, ablation of PPAR γ in SMC (SMC- PPAR $\gamma^{-/-}$ mice) results in an expansion of carotid artery lesion formation due to increased inflammatory cell attachment and TNF- α expression when these carotid arteries had been transplanted to CBA/CaJ recipient mice [24]. In the carotid artery of SMC- PPAR $\gamma^{-/-}$ mice, VCAM-1 expression as well as NF- κ B activation are robustly increased at 2 weeks after transplantation. Atherosclerosis is further exacerbated in combined Apolipoprotein E (ApoE)-deficient (ApoE $^{-/-}$) and SMC- PPAR $\gamma^{-/-}$ mice, especially when challenged with a HFD [25]. Surprisingly, the ApoE $^{-/-}$ SMC- PPAR $\gamma^{-/-}$ mice are characterized by a loss of perivascular adipose tissues (PAT), and *in vivo* data suggest that PAT has protective effect on progression of atherosclerosis [25].

Studies from our laboratory, utilizing mice with SMC or EC-specific overexpression of dominant-negative (DN) mutant PPAR γ (P467L or V290M), the same mutations which cause human hypertension and type II diabetes mellitus, confirm that loss-of-function of PPAR γ in the vasculature of ApoE $^{-/-}$ mice results in increased atherosclerosis in response to Western diet [26]. Consistent with other studies, inhibition of PPAR γ activity in these mice leads to increased expression of the NF- κ B target genes VCAM-1 and MCP-1 in the aorta.

PPAR γ has been documented to regulate NF- κ B activity in a variety of cell types, although the precise molecular mechanism remains unclear. Classically, macrophage PPAR γ is known to antagonize the activity of NF- κ B and modify downstream pro-inflammatory signaling cascades through a mechanism called transrepression [19]. In this context, transrepression involves PPAR γ -mediated stabilization of a corepressor complex on the promoters of NF- κ B target genes. Like transactivation, transrepression is ligand dependent. However, unlike transactivation which requires a transcriptional complex consisting of PPAR γ and RXR bound to a PPAR γ binding site called a PPAR response element (PPRE), transrepression does not require RXR or the PPRE. PPAR γ has been reported to inhibit NF- κ B activity by directly interacting and exporting the p65 subunit (RelA) of NF- κ B out of the nucleus [27]. The ubiquitin proteasome system mediates turnover of NF- κ B subunit, p65 by

nuclear E3 ligases [28]. Recently, PPAR γ was reported to act as an E3 ubiquitin ligase with p65 as a target [29●]. PPAR γ has been proposed to contain a RING domain similar to other E3 ubiquitin ligases, and mutation of a critical cysteine residue (C139A) participating in ring formation abolished p65 turnover. The E3 ligase function of PPAR γ has been described in several *in vitro* cancer cell culture models but it remains unknown whether this mechanism is actually involved in the inhibition of tumor growth *in vivo* [29●]. If proven, it would suggest a model by which PPAR γ mediates its anti-inflammatory actions through a mechanism involving ubiquitination and degradation of NF- κ B subunits.

Role of PPAR γ in the Regulation of BP and Vascular Function

TZDs has been reported to reduce BP in human diabetic subjects and in animal models [30, 31], a property not shared by other antidiabetic drugs (metformin, sulfonylurea). The PROactive trial, the largest clinical trial of its kind which measured cardiovascular (CV) endpoints to pioglitazone, reported significantly lower BP, and reduced rates of all-cause mortality, myocardial infarction, and stroke [32, 33]. Loss-of-function mutations in PPAR γ (P467L, V290M, R165T and L339X) lead to severe early-onset hypertension in addition to metabolic abnormalities [4, 3, 34]. Because the cardiovascular and metabolic disturbances occur concurrently in the affected subjects, it has not been possible to assess if the hemodynamic effects of impaired PPAR γ activity are the result of reduced glycemic control or a direct effect of PPAR γ mutations in cardiovascular tissues. For example, studies of kidney-specific PPAR γ knockout mice clearly showed that the detrimental water retention effects of TZDs is due to PPAR γ activation in the collecting duct [35]. Similarly, genetic models consistently demonstrate that both EC and SMC PPAR γ plays a critical role in regulating arterial pressure independently of systemic metabolism. For example, mice harboring the genetically equivalent mutation (P465L) in PPAR γ as patients similarly exhibit hypertension and vascular dysfunction, but are not insulin resistant [36, 37].

A number of research groups have tested the hypothesis that PPAR γ in SMCs regulates arterial pressure. However, there is disagreement in the literature regarding the effect of SMC-specific deletion of PPAR γ on BP. Whereas moderately increased mean arterial pressure was reported in one model [38], hypotension was reported in another [39]. Just as confusing, inducible VSMC-specific inactivation of PPAR γ does not affect BP at baseline, and the BP elevation in response to angiotensin II infusion was equivalent to control mice [40]. The reasons behind the discrepant data in similar models remain unclear. Using an alternative approach mirroring the hypertension observed in human subjects carrying mutations in PPAR γ , we showed that transgenic mice (termed S-P467L) expressing a DN mutation in PPAR γ specifically targeted to VSMCs exhibit cerebral arteriole remodeling, vascular and autonomic dysfunction, and mild hypertension [41–45]. The arterial remodeling is consistent with the observation that in cultured VSMCs, PPAR γ activation inhibits proliferation and migration through mechanisms involved in cell cycle arrest and inhibition of cyclin-dependent kinases [46].

Given that PPAR γ is a transcription factor, we hypothesized that the physiological effects of PPAR γ -deficiency (in knockout mice) or PPAR γ -interference (in mice carrying disease-causing PPAR γ mutations) were due to alterations in expression of PPAR γ target genes.

Thus, we have focused on elucidating the transcriptional targets of PPAR γ in VSMCs. Studies of S-P467L mice led to the identification of two novel PPAR γ target genes, which regulate vasomotor function. S-P467L mice are characterized by enhanced myogenic tone in mesenteric artery [44], and impaired nitric oxide (NO)-mediated vasodilation, enhanced agonist-induced constriction in both aorta and basilar arteries [42, 45], and augmented myogenic tone in middle cerebral arteries [47]. We showed that enhanced myogenic tone in mesenteric artery is mechanistically due to impaired expression of G-protein signaling 5 (RGS5) which leads to enhanced angiotensin-II signaling, increased protein kinase C activation and impaired BK channel activity [44]. In aorta, DN PPAR γ leads to increased RhoA and Rho kinase activity due to downregulation of cullin-3, the scaffold component of the E3 ubiquitin ligase complex, which links the ubiquitination machinery with the target protein. This linkage requires a substrate recognition protein and cullin-3 adaptor, which are encoded by BTB-domain containing proteins. Interestingly, the loss of cullin-3 activity in S-P467L mice is associated with a robust suppression of a novel PPAR γ target and BTB-domain containing protein, RhoBTB1 [45]. Interestingly, a cullin-3 mutation, characterized by a loss of 57 amino acids encoded by exon 9 (Cul3⁻⁹), has been identified in pseudohypoaldosteronism type II (PHAII) patients with severe early-onset hypertension [48]. Loss of cullin-3 activity leads to decreased WNK4 ubiquitination in the kidney [49●], and decreased RhoA ubiquitination [50]. An animal model expressing the same mutation in cullin-3 non-selectively in all cells exhibits hypertension [51●]. Since increased RhoA activity contributes to hypertension in humans, examining the role of cullin-3 in VSMCs and its effects on vasomotor function and BP regulation is a necessary next step.

Endothelial PPAR γ has been proposed to play a protective role through the regulation of gene targets involved in inflammation, cell adhesion, oxidative stress, and by maintaining a balance between vasodilators and constrictors [52]. EC-specific ablation of PPAR γ in mice results in hypertension only after a challenge with HFD but not at baseline [53]. Interestingly, rosiglitazone treatment fails to improve this HFD-induced hypertension, suggesting that EC PPAR γ plays a critical role in the antihypertensive effects mediated by rosiglitazone. Several groups have used the Tie2 driven Cre-recombinase to delete PPAR γ in EC with the resulting phenotypes ranging from hypertension [54] to moderate hypotension [38]. These discrepancies in BP remain unclear but may be due to activity of Tie2 promoter in tissues other than ECs [55]. To address this limitation, the endothelial-cadherin (cdh5) promoter was used to disrupt EC PPAR γ [56]. The resulting mice exhibit normal BP, however, increased cerebrovascular permeability and brain infarction were observed after focal ischemia, highlighting the protective role of EC PPAR γ in the cerebral circulation.

The importance of PPAR γ activation in EC may be particularly evident during disease conditions. Stressors such as HFD or angiotensin II may be required to unmask the phenotype when investigating EC-specific PPAR γ function. Mice expressing DN PPAR γ mutations (V290M or P467L) specifically in EC are normotensive and exhibit normal endothelial function at baseline. However, an enhanced pressor response to angiotensin II, and profound endothelial dysfunction were observed after a HFD that was mediated by an oxidative stress-dependent mechanism [57]. Similarly, EC-specific deletion of PPAR γ causes endothelial dysfunction after HFD, but not at baseline [58]. Interestingly, this occurred despite reduced adiposity and increased insulin sensitivity. Although these data

suggest that EC PPAR γ integrates metabolic and vascular responses, the contrasting effects on vasoreactivity and metabolism reinforce the possibility that EC PPAR γ regulates vascular tone independent of its metabolic effects.

Adiponectin has been reported to be required for PPAR γ -mediated amelioration of endothelial function [59]. Adiponectin, a protective adipokine and PPAR γ target, is a secretory protein derived from adipose tissue that exerts multiple beneficial effects on the cardiovascular system. Rosiglitazone mitigates aortic endothelial dysfunction in both db/db and HFD-induced obese mice, but not in adiponectin knockout mice. In the aorta, adiponectin increases NO bioavailability and reduces oxidative stress through AMPK and PKA signalling [59]. It remains controversial whether adiponectin is produced in tissues other than adipose. Recent evidence shows that adiponectin protein is expressed in mouse aortic ECs [60]. High level of perivascular but not circulating adiponectin, was positively correlated with endothelial NO synthase uncoupling and superoxide expression in human atherosclerotic vessels [61]. The authors demonstrate that this occurs through a PPAR γ -dependent mechanism, suggesting that perivascular adiponectin has a protective effect during a vessel redox state. It will be important to investigate whether endothelial adiponectin is the primary mediator of the protective role PPAR γ in EC.

Role of PPAR γ in the Central Nervous System Control of Metabolism

The improvement of glycemic control and unparalleled ability to prevent the occurrence of T2DM conferred by TZDs are unfortunately accompanied by augmented food intake, body weight and body fat gain both in humans and in rodent models [62, 63]. Consistent with the critical role of PPAR γ in adipogenesis [64–66], the prevailing thinking has been that the TZD-associated weight gain is largely due to increased deposition of lipids and enhanced adipogenic capacity of white adipose tissue following PPAR γ activation [67]. Inconsistent with this thinking is data showing that constitutive activation of PPAR γ in adipocytes is sufficient for systemic insulin sensitization which occurs without concomitant weight gain [68]. This implies that non-adipose tissues may be the actual targets mediating the insulin-sensitization and adverse effects of TZDs. Indeed, TZDs have been demonstrated to improve insulin sensitivity in mice completely lacking adipose tissue [69] or with adipose-specific deletion of PPAR γ [70].

Increased appetite has been reported in patients after 4 weeks of troglitazone treatment [63]. Reduced systemic levels of leptin, a critical anorexigenic signal to the hypothalamus, was concluded to have caused hyperphagia in these patients [63]. Not recognized at the time, reports of “increased hunger” perhaps constituted the first clue that TZD-mediated target activation in the CNS may account for weight gain. Consistent with this, TZDs can cross the blood-brain barrier [71] and PPAR γ is expressed in regions of the hypothalamus critical for energy balance, particularly the neurons of the arcuate nucleus [72]. In 2011, several groups reported evidence that the activation of brain PPAR γ leads to changes in energy balance and feeding behavior. First, activation of hypothalamic PPAR γ leads to increased food intake and body fat gain in rats, whereas blocking PPAR γ completely attenuates the rosiglitazone-induced food intake [73]. This implies that modulation of hypothalamic PPAR γ leads to changes in feeding behavior and results in overall energy imbalance. Second, mice lacking

PPAR γ in neurons of the brain (N- PPAR $\gamma^{-/-}$ mice) exhibited reduced food intake and increased energy expenditure, leading to protection against diet-induced obesity (DIO) [74]. Interestingly, the rosiglitazone-induced hepatic insulin receptor signal transduction is completely abolished in the N-PPAR $\gamma^{-/-}$ mice, suggesting that brain PPAR γ plays a critical role in liver-mediated insulin sensitivity. The N- PPAR $\gamma^{-/-}$ mice also have increased sensitivity to the anorexigenic adipokine leptin [75], a finding corroborated by pharmacological inhibition of hypothalamic PPAR γ [73]. Two groups independently reported that activation of brain PPAR γ promotes TZD-associated weight gain by depressing energy expenditure, increasing food intake and fat accumulation [73, 74]. The finding that brain PPAR γ is required in part for the TZD-mediated hepatic insulin sensitization has significant therapeutic implications as amelioration of weight gain effects of TZD cannot be achieved by simply restricting access to the brain of drugs that activate PPAR γ , since this may interfere with the anti-diabetic properties of these drugs [76].

The pro-opiomelanocortin (POMC) and agouti-related peptide/neuropeptide Y (AgRP/NPY) expressing neurons are arcuate nucleus substrates of the central melanocortin system [77] and play a critical role in the maintenance of energy balance [78]. Activation of brain PPAR γ decreases the formation of reactive oxygen species (ROS) in the arcuate nucleus of mice [79]. Mechanistically, this leads to inhibition of POMC and increase of AgRP/NPY firing rate, implicating PPAR γ as a critical regulator of the activity of these neurons. Suppression of PPAR γ restores ROS levels in POMC and AgRP/NPY neurons, reverses HFD-induced impairment of AgRP and POMC firing, and ultimately leads to decreased caloric intake in DIO mice. These findings suggest a role for hypothalamic PPAR γ as a nutritional sensor, which modulates the firing pattern of POMC and AgRP/NPY neurons via ROS levels to affect feeding behavior. More recently it was shown that POMC neurons are sufficient to mediate the effect of PPAR γ in the brain on systemic energy homeostasis [80●]. Mice lacking PPAR γ specifically in POMC neurons (POMC- PPAR $\gamma^{-/-}$) are resistant to weight gain as a result of reduced caloric intake, adipose accumulation, and increased energy expenditure, and do not gain weight in response to peripheral administration of rosiglitazone. Thus, POMC neurons are necessary and sufficient for mediating the weight gain caused by TZD. The authors, however, did not test whether POMC PPAR γ is required for the insulin sensitizing effects of TZDs in the liver. Perhaps this is because the POMC-specific PPAR γ ablation led to a significantly greater baseline insulin sensitivity. The question remains, however, whether the increased insulin sensitivity at baseline is still intact in conditions of HFD.

The role of PPAR γ in AgRP/NPY neurons has only recently been investigated. Starvation causes a significant increase in AgRP mRNA in the arcuate nucleus with a concomitant increase in PPAR γ expression specifically in the AgRP/NPY neurons [81●]. The authors speculate that the upregulation of AgRP is a PPAR γ -dependent process since peripheral administration of the PPAR γ antagonist GW9662 blocks starvation-induced increases in both PPAR γ and AgRP mRNA.

The idea that brain PPAR γ modulates metabolic functions previously ascribed largely to adipocytes has led to a significant shift in our understanding of PPAR γ biology. We now know that TZDs as well as HFD activate brain PPAR γ and result in increased caloric intake

and body weight gain. This has important implications in the face of escalating global obesity as targeting PPAR γ remains the standard in treating metabolic diseases.

New Therapeutic Interventions Targeting PPAR γ

The ubiquitous expression of PPAR γ places the receptor at a unique position to exert direct biological effects on multiple organ systems, including cardiovascular, nervous, immune, and gastrointestinal. This, however, also accounts for the undesired effects observed with TZD-mediated activation. The use of TZDs is associated with serious side effects such as weight gain [73, 74], fluid retention and edema [82], bone fractures [83], and bladder cancer [84], which have led to a significant decrease in prescription of these drugs. Modulation of PPAR γ activity through targeted protein modifications raises the exciting possibility of tissue-selective activation and elimination of such off-target effects. This has fueled a significant interest in the development of selective PPAR γ modulators (SPPARMs) which lower glucose levels and improve insulin resistance without the adverse effects [85].

Spiegelman's group first reported that phosphorylation of PPAR γ at Ser273 in adipocytes by inflammatory cytokine and free fatty acids (FFAs) is blocked by TZDs [86]. The group developed a new compound, SR1664, which selectively inhibits Ser273 phosphorylation [87], with a resulting improvement in insulin resistance in DIO mice. The preservation of PPAR γ activity by blocking Ser273 phosphorylation results in activation of a much smaller subset of genes than by TZD-mediated transactivation. Interestingly, there were fewer side effects in SR1664-treated mice than rosiglitazone-treated mice. Two additional compounds, GQ-16 [88] and F12016 [89], have been reported to have similar properties, supporting the hypothesis that selective inhibition of Ser273 phosphorylation eliminates side effects but retains insulin-sensitizing characteristics.

Other post-translational modifications of PPAR γ have been reported to influence its activity. For example, PPAR γ can be acetylated at Lys268 and Lys293, and TZD-mediated deacetylation of these sites by the NAD-dependent deacetylase, SirT1 leads to an increase in selective brown adipose tissue genes and concomitant decrease in white adipocyte genes [90, 91], and an enhancement of energy expenditure and insulin sensitivity in adipocyte tissue [92]. Sumoylation of PPAR γ at Lys107 leads to increased co-repressor binding and inhibition of target gene transcription [93]. Little is currently known whether similar alterations affects PPAR γ function in other tissues including the cardiovascular, immune or nervous systems. Identification of mechanisms leading to tissue-specific changes in PPAR γ activity can lead to the development of targeted treatments that are characterized by little or no deleterious effects.

Conclusion

Proper function of PPAR γ is critical for the maintenance of both vascular and metabolic homeostasis (Figure). This is evidenced by the observations that loss or gain-of-function mutations in PPAR γ are associated with the development of MetS-like phenotypes as well as hypertension. TZDs previously offered the most effective treatment for metabolic dysfunction, but the ubiquitous transactivation of PPAR γ target genes, led to a number of

serious off target effects. New modulators of PPAR γ activity that alter posttranslational modifications may confer beneficial metabolic and cardiovascular effects with fewer adverse outcomes. Whether posttranslational alterations affect PPAR γ function in a similar way in all tissues remains unknown and a topic for future investigation. Of course, the recently discovered role for PPAR γ in the brain in mediating susceptibility to diet induced obesity presents a major therapeutic challenge that will have to be considered in any novel therapy.

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Figure. Role of PPAR γ in Brain and Artery.

PPAR γ is activated by synthetic agonists such as thiazolidinediones (TZD) or endogenous fatty acids of lesser known origin. PPAR γ function is inhibited by inactivating or dominant negative mutations which cause hypertension and dyslipidemia. PPAR γ has well known antioxidant properties by the induction of reactive oxygen scavengers and the inhibition of enzymes which produce reactive oxygen species. This results in increases and decreases in specific neuronal populations which leads to increased food intake and weight gain, a common adverse effect of TZDs. In the blood vessel, PPAR γ activity is anti-oxidant and anti-inflammatory and thorough actions regulating NO and RhoA promotes vasodilation while inhibiting vasoconstriction.