

REVIEW

The Role of PPAR γ in Cardiovascular Diseases

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Summary

The peroxisome proliferator-activated receptors (PPAR) belong to the nuclear superfamily of ligand-activated transcription factors. PPAR γ acts as a nutrient sensor that regulates several homeostatic functions. Its disruption can lead to vascular pathologies, disorders of fatty acid/lipid metabolism and insulin resistance. PPAR γ can modulate several signaling pathways connected with blood pressure regulation. Firstly, it affects the insulin signaling pathway and endothelial dysfunction by modulation of expression and/or phosphorylation of signaling molecules through the PI3K/Akt/eNOS or MAPK/ET-1 pathways. Secondly, it can modulate gene expression of the renin-angiotensin system – cascade proteins, which potentially slow down the progression of atherosclerosis and hypertension. Thirdly, it can modulate oxidative stress response either directly through PPAR or indirectly through Nrf2 activation. In this context, activation and functioning of PPAR γ is very important in the regulation of several disorders such as diabetes mellitus, hypertension and/or metabolic syndrome.

Key words

PPAR γ • Hypertension • Oxidative stress • Antioxidant response • Renin-angiotensin system • Nitric oxide

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Introduction

Peroxisome proliferator-activated receptors (PPAR) belong to the nuclear superfamily of ligand-activated transcription factors. The name of this group of nuclear receptors was derived from their ability to stimulate proliferation of peroxisomes in rats (Issemann and Green 1990). In humans, three isoforms of nuclear receptors were discovered: PPAR α , PPAR β/δ and PPAR γ , which differ in their distribution and specific function (Leonardini *et al.* 2009). PPAR activation leads to transactivation and transrepression of selected gene expression. Ligand-activated PPAR creates heterodimer with the retinoic X receptor, which is subsequently bound on sequence-specific target element in promotor region of target genes (Oyekan 2011).

PPARs are nutrient sensors that regulate a number of homeostatic functions, such as glucose and lipid metabolism by uptake, utilization, oxidation and storage of fatty acids. It was found that PPAR γ as a nutrient-sensing signaling sensor can influence nutritional programming of hypertension and metabolic syndrome (Tain *et al.* 2016). PPARs participate in the regulation of cell growth, migration and apoptosis and they may modulate oxidative stress, antioxidant response and inflammatory diseases in cardiovascular system (Chen *et al.* 2008, Oyekan 2011, Polvani *et al.* 2012). Disruptions of these pathways can result in the development of several diseases and pathological states, such as obesity, obesity-induced inflammation, atherosclerosis, diabetes mellitus, metabolic syndrome and hypertension (Duan *et al.* 2009, Oyekan 2011, Kiss *et al.* 2013, Montanez *et al.* 2013).

Post-translational modifications of PPAR γ

Up to this day, seven diverse mRNA transcripts of PPAR γ (γ 1- γ 7) were found, which are generated with different initiation types and alternative splicing of exons – five exons in terminal region (Chen *et al.* 2006, Christodoulides and Vidal-Puig 2010) and six exons in the open reading frame. Only PPAR γ 1 is expressed in heart and skeletal muscle, vascular smooth muscle cells and endothelial cells (Das and Chakrabarti 2006, Chen *et al.* 2006, Li and Wang 2007), while isoforms PPAR γ 2 or PPAR γ 4 are primarily delimited in adipose tissue or freely presented in macrophages, colon and in adipocytes (Chen *et al.* 2006).

The action of PPAR γ is regulated by post-translation modifications such as phosphorylation, acetylation, SUMOylation and/or ubiquitination that represent a potentially distinct feature of PPAR γ and could be exploited for tissue-specific distribution and function (van Beekum *et al.* 2009). Phosphorylation by MAPK inhibits ligand binding (Hu *et al.* 1996, Zhang *et al.* 1996, Camp and Tafuri 1997) or increases the activity of PPAR γ by the cyclin-dependent kinases (Compe *et al.* 2005, Iankova *et al.* 2006).

Likewise, PPAR γ activity regulation is controlled by covalent attachment of small ubiquitin-like modifier (SUMO). SUMOylation is one of the post-translational modification responsible for the regulation of stability, nuclear-cytosolic distribution and activity of transcription factors at different Lys residues (Pascual *et al.* 2005, Shimizu *et al.* 2006, Kim *et al.* 2013).

Ubiquitination is yet another level of control over PPAR γ activity. In the nucleus of adipocytes, the PPAR γ 2 protein level is decreased by the action of thiazolidinediones (TZDs). The degradation occurs in an ubiquitin-dependent manner in the AF-2 domain of PPAR γ . However, the AF-1 domains of PPAR γ 1 and PPAR γ 2 are degraded by the REG γ proteasome, the type of proteasome that degrades the target substrate in an ubiquitin- and ATP-independent fashion. The PPAR γ protein (with a short half-life time of ~2 hours) is polyubiquitinated and subsequent degraded by the proteasome (Hauser *et al.* 2000).

PPAR γ -deficient and transgenic mice

Human genetic studies have revealed that PPAR γ mutation in humans can result in either a gain or a loss of function. Pro¹²Ala mutation can result in a loss

of function mutation and has been reported to be associated with increased protection against insulin resistance and diabetes type 2 (Mori *et al.* 2001, Lindi *et al.* 2002) and a decreased incidence of myocardial infarction and/or lower diastolic blood pressure (BP) (Ostgren *et al.* 2003). On other hand, several other mutations such as Pro⁴⁶⁷Leu, Val²⁹⁰Met, Phe³⁸⁸Leu and Arg⁴²⁵Cys are all involved in loss of function mutations and have been associated with partial lipodystrophy, insulin resistance, diabetes and hypertension (Barroso *et al.* 1999, Agarwal and Garg 2002, Hegele *et al.* 2002). The ligand binding domain mutants of PPAR γ with dominant negative actions stimulate associations with the nuclear receptor corepressor (N-CoR) and the silencing mediator of retinoid and thyroid receptors (SMRT) and they inhibit activities of all three PPAR isoforms (Semple *et al.* 2005).

It was shown that PPAR γ is required for placental, cardiac and adipose tissue development. PPAR γ null mouse surviving to term following placental reconstitution exhibited a phenotypic array that included lipodystrophy, fatty liver and hemorrhages, with fatal consequences during the first week of life (Barak *et al.* 1999). Increased cardiac hypertrophy and/or blood pressure decrease were observed in cardiac knockout mice or generalized knockout mice (Duan *et al.* 2005, Duan *et al.* 2007)

PPAR γ and mechanisms of blood pressure regulation in hypertension and metabolic syndrome

Activation of PPAR γ plays an essential role in the regulation of eNOS expression in endothelial cells and increases bioavailability of the nitric oxide (NO) (Nagao and Yamaguchi 2012). Vascular PPAR γ is known also as peripheral regulator of the cardiovascular rhythm. PPAR γ controls circadian variation in blood pressure and heart rate *via* the BMAL-1 (Brain and muscle Arnt-like protein-1) protein (Wang *et al.* 2008) and is an important component of the “vascular clock”. Pioglitazone (PIO), the PPAR γ agonist, modifies BP circadian rhythm in patients with diabetes mellitus type 2 from non-dippers (patients without 10 % BP decrease at night) to dippers (patients with 10 % or higher BP decrease at night) (Anan *et al.* 2007). PPAR γ can play an important role in the regulation of vascular homeostasis. Disruption of PPAR γ function in these processes can contribute to vascular pathologies, such as atherosclerosis, restenosis and

hypertension (Li and Wang 2007, Burris *et al.* 2012).

It was found that TZDs can decrease BP in non-diabetic hypertensive patients (Raji *et al.* 2003) as well as in diabetic patients (Shargorodsky *et al.* 2003). Moreover, TZDs improve endothelial dysfunction in rat mesenteric resistance arteries after angiotensin II (Ang II) infusions (Diep *et al.* 2002). The beneficial pleiotropic action of PPAR γ on the vasculature are glycemia-independent (Sugawara *et al.* 2010). This effect can occur *via* several mechanisms comprising PPAR γ -mediated modulation of expression and/or phosphorylation of specific signaling molecules of the insulin signaling pathway. This PPAR γ -dependent modulation of insulin receptor signaling can lead to re-establishment of the balance between PI3K/Akt/eNOS and MAPK/ET-1, with a subsequent increase of NO bioavailability and vasodilatation (Li and Wang 2007).

Furthermore, PPAR γ can directly modulate gene expression of antioxidant and prooxidant genes and maintain redox homeostasis *via* interaction between PPAR γ and the signaling pathways involved in oxidative stress modulation. It is an example of cooperation of signaling pathways, such as Nrf2 (Nuclear factor E2-related factor 2), NF- κ B (nuclear factor kappa B), Wnt (Wingless-type MMTV integration site)/ β -catenin and FOXO (forkhead box protein O) proteins (Polvani *et al.* 2012). PPAR γ activation can decrease oxidative stress in rostral ventrolateral medulla, which plays a critical role in pathogenesis of hypertension (Chan *et al.* 2010). Modulation of oxidative stress can slow down the development of hypertension in the prehypertensive period (Dovinova *et al.* 2013).

In addition, PPAR γ can inhibit gene expression of the AT $_1$ receptor and, through Ang II, induce ERK 1/2 activation and subsequent inhibition of vascular remodeling (Benkirane *et al.* 2006). PPAR γ activation can inhibit the renin-angiotensin system (RAS) and decrease BP (Roszer and Ricote 2010).

PPAR γ and the PI3K/Akt/eNOS signaling pathway

Insulin resistance is the reduction of sensitivity and/or response to metabolic activation of the insulin receptor and is associated with a variety of metabolic disease and hemodynamic disruptions. A reciprocal relationship between insulin resistance and endothelial dysfunction was observed in animal experimental models and in human studies (Koh *et al.* 2005, Koh *et al.* 2006).

Insulin plays an essential role in the control of glucose homeostasis in skeletal muscles, adipose tissue and liver. It is involved in blood flow regulation and maintenance of vascular health. The most important effect of insulin on the cardiovascular system is the stimulation of NO production in the vascular endothelium. Abnormal reduction of insulin sensitivity affects vascular homeostasis, with manifestations such as impaired endothelial function, vasodilation, enhanced vascular inflammation and atherosclerotic lesion formation.

Insulin is synthesized in pancreatic β -cells in the islets of Langerhans in response to increased glycemia after a meal from a precursor – preproinsulin (Sharma *et al.* 2008). Preproinsulin, 110-amino acids long, contains an N-terminal signal peptide that facilitates transfer of signal recognition particles into the lumen of the rough endoplasmic reticulum. The signal peptide of preproinsulin is subsequently cleaved away by a signal peptidase into proinsulin. Proinsulin folds in the oxidizing environment and the folded proinsulin is transported to the Golgi apparatus in immature secretory vesicles where it is cleaved down to insulin and C-peptide (Fu *et al.* 2013). The insulin signaling pathway is activated through insulin binding to the insulin receptor (IR). The binding of insulin leads to conformation changes in the intrinsic tyrosine kinase of β transmembrane subunits of the insulin receptor as well as the tyrosine phosphorylation of multiple docking proteins, including insulin receptor substrates 1 (IRS1) and 2 (IRS2) (Fig. 1a). IRS1 is necessary for insulin-stimulated NO production in the endothelium. IRS1 and IRS2 are not functionally redundant, although they both activate many similar downstream pathways (Waters and Pessin 1996, Hanke and Mann 2009). IRS2 may contribute to NO production, but is primarily implicated in the delivery of insulin to skeletal muscle interstitium (Arce-Esquivel *et al.* 2013).

IRS2 is a widely expressed protein that regulates crucial biological processes including glucose metabolism, protein synthesis and cell survival. IRS2 is a part of the insulin signaling pathway and mediates the activation of the NO or ET-1 through PI3K/Akt or Ras/MAPK in insulin target tissues and in the pancreas (Oliveira *et al.* 2014). The role of the muscle vasculature is beginning to be appreciated as a factor that influences the myocyte response to insulin. Insulin signaling plays a critical role in glucose disposal in skeletal muscle (DeFronzo *et al.* 1985). In cultured myocytes, insulin

activates insulin receptor and IRS2 proteins and stimulates glucose uptake in within minutes (Sarabia *et al.* 1990, Sarabia *et al.* 1992, Ogihara *et al.* 1997). Loss of skeletal muscle capillary density is observed in both insulin resistance and in type 2 diabetes, while insulin action is positively correlated with capillary density (Lillioja *et al.* 1987). Insulin-stimulated increases in blood flow or increased recruitment of perfused capillaries are both dependent on nitric oxide (NO) production and may augment insulin delivery to the interstitium because NO has been shown to mediate insulin-stimulated capillary recruitment (Kubota *et al.* 2011).

IRS1 or IRS2 phosphorylation leads to the activation of two signaling pathways: PI3K/Akt/eNOS and MAPK/ET-1 (Fig. 1a). The tyrosine phosphorylated

IRS1 activates phosphatidylinositol 3-kinase (PI3K) through phosphorylation of the src homology 2 (SH2) domain of the p85 regulatory subunit of PI3K. Activation of the p110 subunit of PI3K cleaves catalytically the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP₂) to phosphatidylinositol 3,4,5-trisphosphate (PIP₃). PIP₃ is needed for PIP₃-dependent phosphorylation of PDK1 (3'-phosphoinositide-dependent kinase-1) and Akt kinase. Finally, Akt kinase phosphorylates several effector proteins, including GSK-3 β , FOXO and eNOS. GSK-3 β activation is insulin-independent, but it may be activated through the insulin signaling pathway. GSK-3 β phosphorylation through IRS1 activation and PKB inhibition is more present in basal conditions compared to insulin receptor stimulation (Copps and White 2012).

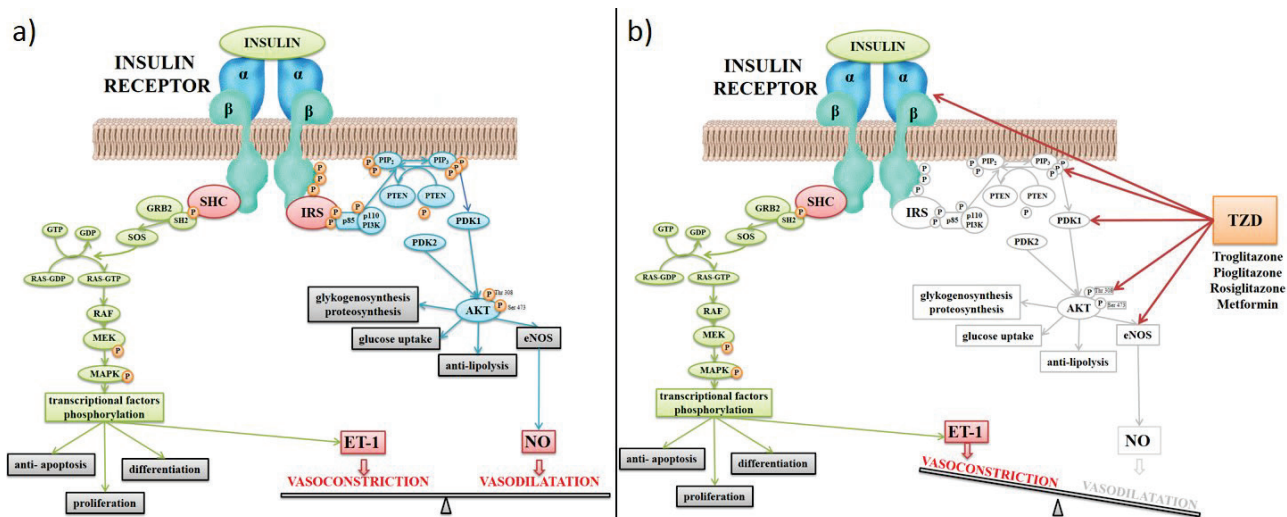


Fig. 1. Activation of the insulin signaling pathway and the effect of TZD-activated PPAR γ . **a)** Activation of the insulin signaling pathway and the effect of insulin on vascular tone. **b)** Activation of PPAR γ by TZDs. PPAR γ activation affects the insulin signaling pathway by modulation of expression and/or phosphorylation of specific signaling molecules, which can lead to reestablishment of balance between the vasodilator and vasoconstrictor effects due to insulin receptor activation resulting in an improvement of insulin sensitivity.

PI3K/Akt/eNOS signaling pathway is critical point for vascular tone regulation, because eNOS catalyzes the conversion of L-arginine to L-citrulline and produces NO. On the other hand, MAPK cascade activation plays an important role in insulin-regulated mitogen processes, such as cell proliferation, cell differentiation and cell survival (Kim and Choi 2010).

The balance between vasodilator and vasoconstrictor effects induced by the activation of insulin receptor is disrupted in vascular endothelium cells of insulin resistance animal models. PI3K/Akt/eNOS signaling pathway is suppressed while signaling pathway MAPK/ET-1 is preserved (Kobayashi *et al.* 2004). This

balance disruption is called endothelial dysfunction (Mitchell *et al.* 2008). TZDs activation of PPAR γ improves insulin sensitivity in diabetic patients, leading to the reduction of plasma insulin and glucose levels (Fig. 1b). PPAR γ activation affects insulin signaling pathway by modulation of expression and/or phosphorylation of specific signaling molecules, which can lead to reestablishment of balance between vasodilator and vasoconstrictor effects due to insulin receptor activation.

Li *et al.* (2010) showed that PI3K expression and phosphorylation of PKB-eNOS in vascular tissues is decreased in the young male spontaneously hypertensive

rats (SHR). Administration of rosiglitazone (RSG) raises vascular PPAR γ expression, resulting in restoration of PI3K/PKB/eNOS signaling activation, followed by the improvement of endothelial function in the young SHR due to increased NO release (Li *et al.* 2010).

In clinical practice, synthetic ligands are used. Synthetic PPAR γ ligands are TZD derivatives. They are selective agonists of nuclear receptor PPAR γ and they are used for insulin sensitivity improvement in patients with diabetes mellitus type 2 (Nakamura *et al.* 2000, Fruchart *et al.* 2001, Taniguchi *et al.* 2001), while TZDs activate minimally PPAR- α and PPAR- β isoforms (Willson *et al.* 1996). TZDs treatment can influence and change the expression of signaling molecules of the insulin signaling cascade (IRS, PI3K, Akt, eNOS, 5'-AMP kinase, GLUT4, etc.) connected with improvement of insulin sensitivity and/or endothelial dysfunction.

TZDs comprise troglitazone, rosiglitazone, pioglitazone and tideglusib. Troglitazone was approved in 1997, but it was withdrawn from the market for increased risk of liver failure and extensive hepatotoxicity in 2000 (Kohlroser *et al.* 2000). Tideglusib is a potent, irreversible, non ATP-competitive glycogen synthase kinase-3 β (GSK-3 β) inhibitor and PPAR γ agonist tideglusib seems to be suitable candidate for Alzheimer disease treatment or for a treatment of stroke (Armagan *et al.* 2015), but its application in cardiovascular disease treatment has not been examined yet.

The effectiveness of other two TZDs pioglitazone and rosiglitazone are similar in treatment of diabetes mellitus type 2, but they differ in the treatment of cardiovascular diseases. The PROactive study points out the positive effect of PIO (reduced cardiovascular complications by 16 %) in cardiovascular disease patients (Dormandy *et al.* 2009), while RSG treatment was associated with increased incidence of myocardial infarction and death after a relatively short-term exposure (Nissen and Wolski 2007). The European Medicines Agency withdrew its approval of this medication in 2010 due to cardiovascular safety concerns (Krishnaswami *et al.* 2010).

PPAR γ in adipose tissue and insulin resistance

PPAR γ has tissue-specific effects. It is most highly expressed in adipose tissue. PPAR γ upregulates genes involved in glucose uptake and also controls the expression of factors secreted by adipocytes in adipose tissue. PPAR γ activation enhances the uptake and

sequestration of fatty acids in adipose tissue and improves insulin resistance (Ahmadian *et al.* 2009). Members of the fibroblast growth factor family (FGF1 and FGF21) act locally in adipose tissue to mediate the physiological and pharmacological actions of PPAR γ and to promote insulin sensitization in response to high-fat diet (Dutchak *et al.* 2012, Jonker *et al.* 2012, Sun and Scherer 2012). FGF binding to FGF receptors induces the activation of four key intracellular signaling pathways: RAS/RAF/MAPK, PI3K/Akt, STAT and PLC γ (Beenken and Mohammadi 2009).

FGF21 is a key mediator of fatty acid oxidation and lipid metabolism. Pharmacological doses of FGF21 improve glucose tolerance, lower serum free fatty acids and lead to weight loss in obese mice. However, the expected beneficial effects of endogenous FGF21 to increase glucose tolerance and reduce circulating triglycerides are absent in obesity and leads to FGF21-resistant state (Fisher *et al.* 2010).

In the development of cardiovascular diseases including atherosclerosis, coronary heart disease, myocardial ischemia, cardiac hypertrophy and diabetic cardiomyopathy, there is a strong evidence showing that the development is associated with an increase in serum FGF21 levels. This was regarded as a compensatory response to induced cardiac protection. Furthermore, administration of FGF21 suppressed the above cardiovascular diseases. Mechanistic studies revealed that FGF21 induced cardiac protection likely by preventing cardiac lipotoxicity and the associated oxidative stress, inflammation and apoptosis (Cheng *et al.* 2016).

PPAR γ and endothelial nitric oxide synthase

The regulation of eNOS expression and its activation is influenced by various cellular events, such as transcription regulation, protein-protein interaction, phosphorylation and dephosphorylation at different amino acid sequences of eNOS regulated by various kinases and phosphatases (Govers and Rabelink 2001). eNOS has a few well-described phosphorylation/dephosphorylation sites, such as Ser¹¹⁷⁷ and Thr⁴⁹⁵. Some other sites regulating NOS activity (Ser⁶³³, Ser¹¹⁴ and Ser⁶¹⁵) have been identified, but their precise roles remain controversial (Mount *et al.* 2007). These phosphorylation/dephosphorylation regulatory eNOS sites can be activated by multiple protein kinases, including PKA, PKB, PKC, AMPK, ERK and phosphatases such as protein phosphatase (PP)1 and

PP2A in response to multiple stimuli *via* shear stress, growth factors, insulin, etc. (Fleming *et al.* 2001, Mount *et al.* 2007, Chen *et al.* 2009, Xiao *et al.* 2011).

Recent studies have suggested a potential regulatory role of PPAR γ -dependent eNOS expression and NO generation in the vascular endothelium. Several studies suggest that a direct transcriptional mechanism can be involved in PPAR γ -mediated release of NO in endothelial cells. The activation of PPAR γ using 15d-PGJ2 or ciglitazone stimulates NO release from the endothelium (Calnek *et al.* 2003). Mechanisms of PPAR γ activation-mediated increase in endothelial NO production are not yet understood.

Polikandriotis *et al.* (2005) suggested that PPAR γ -dependent eNOS activation is mediated *via* hsp90-dependent mechanism. RSG and 15d-PGJ2 stimulated hsp90-eNOS interaction, resulting in eNOS activation (at Ser¹¹⁷⁷ phosphorylation). Conversely, ciglitazone did not have this effect, which suggests different effects of PPAR γ agonists. It seems that hsp90 probably plays a key role in this context because coadministration PPAR γ agonist with geldanamycin (inhibitor of hsp90) attenuates eNOS activation and NO release from endothelial cells (Polikandriotis *et al.* 2005).

PPAR γ activation decreases expression of NADPH oxidase subunits such as Nox1, gp91phox (Nox2) and Nox4, which is accompanied by an enhanced expression of SOD (superoxide dismutase) resulting in reduction of oxidative stress in the membrane of human umbilical vein endothelial cells. The elevated vascular oxidative stress reduces endothelial bioavailability of NO through peroxynitrite generation. Hwang *et al.* (2005) suggest that, NO release from endothelium due to PPAR γ activation could enhance NO bioavailability by reducing endothelial superoxide anion and oxidative stress.

Endothelial dysfunction can be influenced with adiponectin. This hormonal protein, secreted in adipose tissue, can improve endothelial function *via* PPAR γ activation-mediated eNOS phosphorylation. RSG administration to the diabetic mouse leads to the enhancement of NO bioavailability and the improvement in endothelial function through adiponectin release and subsequently activation of AMPK/eNOS and cAMP/PKA signaling pathways in the aorta (Wong *et al.* 2011).

Rho-kinase plays an important role in endothelial dysfunction development. This serine threonine kinase inactivates eNOS and reduces NO bioavailability (Budzyn *et al.* 2006, Nohria *et al.* 2006). PPAR γ activation inhibits up-regulation of protein

tyrosine phosphatase-2 (SHP-2) Rho-kinase. PIO administration in Ang II-treated cultured rat aortic smooth muscle cells up-regulates SHP-2 and subsequently dephosphorylates a GTP/GDP exchange factor of Rho-kinase Vav, resulting in the inactivation of Rho-kinase (Wakino *et al.* 2004).

Several studies suggest that PPAR γ plays a distinctive role in regulation of eNOS expression in the endothelium, resulting in enhanced generation of vascular NO. PPAR γ activation mediates vascular anti-inflammatory and antioxidant response and regulates endothelial function. Therefore, it has a beneficial effect on the vascular function in patients with atherosclerosis and hypertension with or without diabetes mellitus (Polikandriotis *et al.* 2005, Duan *et al.* 2009, Yu *et al.* 2010). Moreover, the therapeutic opportunities of agents that activate PPAR γ in preventing vascular endothelial dysfunction and cardiovascular disorders associated with endothelial dysfunction are discussed.

PPAR γ and renin-angiotensin system

One PPAR γ -dependent mechanism, which can influence hypertension development, is the attenuation of AT₁ receptor gene expression (Diep *et al.* 2002, Benkirane *et al.* 2006, Sugawara *et al.* 2010). This gene suppression of AT₁ receptor is a result of protein-protein interaction between nuclear receptor PPAR γ and Sp1 protein (specificity protein 1 transcription factor). Sp1 belongs to the class of zinc-finger motifs presented in transcription factors, which can join to GC rich promotor regions. PPAR γ either down-regulates the expression of AT₁ receptor and/or inhibits signaling pathways, such as PI3K and MAPK, through Ang II, PI3K and MAPK, suppressing thus ultimately the activation of RAS cascade (Wu *et al.* 2004, Benkirane *et al.* 2006) and remodeling of vascular wall (Benkirane *et al.* 2006).

RAS is an endocrine system that plays an essential role in cardiovascular and renal physiology. RAS regulates BP and the concentration of sodium ions (Rodrigues-Ferreira and Nahmias 2015). It also influences the sympathetic nervous system (SNS) functions and regulates extracellular fluid volume (Majzunova *et al.* 2013). Dysregulation of RAS participates in the pathogenesis of hypertension, atherosclerosis, ischemic heart disease and heart failure. Physiologically, the effect of RAS is mediated through Ang II, which is generated by an enzyme cascade and released to systemic circulation (Crowley and Coffman 2012). When BP in renal arteries

decreases, cells of the juxtaglomerular apparatus produce and secrete a protease renin (43 kDa). Renin is an endopeptidase and cleaves angiotensinogen to the decapeptide Ang I (angiotensin I). Elevated angiotensinogen concentration leads to supernormal Ang II production (Kobori *et al.* 2007). Ang II is a major stimulator of synthesis and secretion of aldosterone and activates SNS (Fleming *et al.* 2005). It is a mediator of oxidative stress, stimulates the production of cytokines, synthesis of adhesive molecules and stimulates vascular remodeling. Production of Ang II in the heart and in the vascular system significantly contributes to the pathogenesis of the cardiovascular diseases. Except for Ang II, Ang 1-7 (angiotensin 1-7) can be produced from Ang I through “alternative RAS axis”. This alternative Ang 1-7 production is catalyzed by angiotensin-converting enzyme 2 (ACE2) (Santos *et al.* 2013).

Ang II binds to AT₁ or AT₂ receptors. They are associated with GPCR (G protein-coupled receptors). Similarly, it is associated with GPCR Mas receptor. Ang 1-7 is bound to Mas receptor. Activation of these receptors results in the phosphorylation of different signaling pathways, which often leads to opposite cellular roles. ACE/Ang II/AT₁ cascade mediates the major effects of Ang II. Activation of AT₁ receptors stimulates L-type of calcium channels and through G-protein leads to activation of NADPH oxidase and to vasoconstriction response (Buchanan *et al.* 1995). Activation of ACE/Ang II/AT₂ cascade plays a role especially in prenatal period, when this cascade activation acts counter-regulatory to AT₁ receptor. Activation of AT₂ receptors results in anti-proliferative effect and leads to vasodilatation (Carey *et al.* 2000).

An increased expression of various components of the RAS during hypertension has been described in detail by Zicha *et al.* (2014). Several kinases are activated through Ang II-activated AT₁ receptor, e.g. MAPK, p70S3 kinase, etc. This kinase activation is associated with BP increase and with hypertension development. AT₁ receptor activation stimulates NADPH oxidase in vascular wall, which is major source of reactive oxygen species (ROS) (Touyz and Schiffrin 1999).

Gene expression of RAS molecules can be modulated also by PPAR (Fig. 2). PPAR γ is expressed in the juxtaglomerular apparatus cells. Endogenous and pharmacological PPAR γ ligands stimulate renin gene expression (Roszer and Ricote 2010).

Ligands of PPAR γ can suppress the gene expression of ACE in vascular tissues (Efrati *et al.* 2007,

Takai *et al.* 2007, Song *et al.* 2008). In streptozotocin-induced diabetes in rats, bezafibrate and PIO can equally protect against the streptozotocin-induced up-regulation of ACE in the aortic wall. Similarly, ACE gene expression is reduced by chronic treatment with RSG in obese Zucker rats (Song *et al.* 2008). Clinical studies have demonstrated that telmisartan inhibits ACE and blocks AT₁ receptor, resulting in the vascular protection conferred to hypertensive type 2 diabetic patients by the anti-inflammatory and antiatherogenic consequences of PPAR activation (Unger and Stoppelhaar 2007).

Two Ang II receptor blockers, telmisartan and irbesartan, act as selective PPAR modulators (Sanchez *et al.* 2008, Tagami *et al.* 2009). Partial PPAR agonist telmisartan inhibits vascular ACE activity (Takai *et al.* 2007), AT₁ receptor expression (Gosse 2006, Imayama *et al.* 2006) and increases endothelial NO synthesis (Kobayashi *et al.* 2008), preventing oxidative stress and endothelial dysfunction more effectively than non-PPAR-agonists among Ang II receptor blockers.

PPAR blocks the action of Ang II by transcriptionally repressing AT₁ receptor gene expression in VSMCs (vascular smooth muscle cells) (Takeda *et al.* 2000, Imayama *et al.* 2006, Sanchez *et al.* 2008, Tagami *et al.* 2009). In addition to its role as a regulator of vascular tone, AT₁ receptor activation contributes to vascular lesions and atherogenesis by promoting VSMC proliferation (Nishijo *et al.* 1998, Wakino *et al.* 2001). Therefore, a suppressed Ang II response can potentially slow the progression of atherosclerosis.

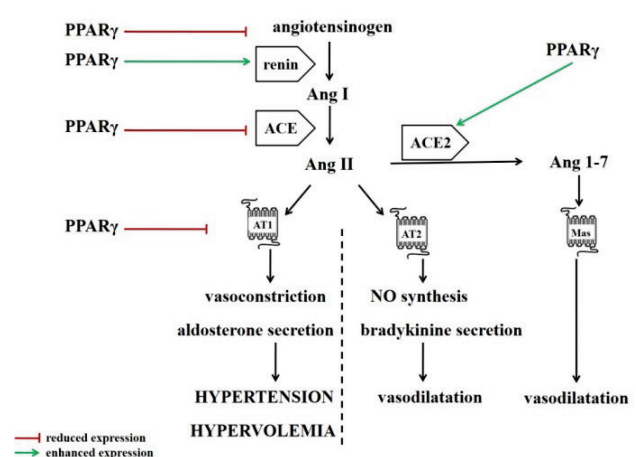


Fig. 2. Role of PPAR γ in the modulation of the RAS cascade, modified according to Roszer and Ricote (2010). Gene expression of RAS molecules is modulated by PPAR γ . Although renin production is facilitated by PPAR γ activation, the hypertensive effects of RAS activation are attenuated by PPAR γ ligands, since these strongly reduce Ang II levels, ACE and AT₁ receptor gene expression.

ACE inhibitor enalapril was tested on PPAR responses. Anthracycline therapy is limited by a cardiotoxicity that may eventually lead to chronic heart failure which is thought to be prevented by ACE inhibitors. Involvement of PPAR and changes in cellular metabolism in anthracycline cardiomyopathy has been investigated after enalaprilat administration to daunorubicin-treated Wistar rats. It was found that anthracycline administration significantly up-regulated PPAR α mRNA in the heart, but did not influence the expression of cardiac PPAR β/δ . In the case of coadministration of ACE inhibitors the expression of cardiac PPAR α mRNA did not change, while the expression of PPAR β/δ was increased. Altered expression of heart PPARs may suggest these nuclear receptors as a novel target in anthracycline cardiomyopathy (Cernecka *et al.* 2013).

Phosphorylation cascades involved in RAS and PPAR γ regulation

Increased phosphorylation of signaling pathways participating on the growth and differentiation of cells is activated through Ang II. Ang II can subsequently activate PI3K and ERK 1/2 kinase and kinase cascades involved in these processes (Touyz and Schiffrin 1999).

PI3K activation *via* Ang II starts with phosphorylation of regulatory subunit 85 α of PI3K. Subsequently, lipid phosphatase SHIP2 (Src homology 2 domain containing inositol 5-phosphatase 2) is activated. PI3K generates PIP3 and subsequently SHIP2 phosphatase hydrolyzes PIP3 to primary lipids, which are needed for activation of Akt kinase (Franke *et al.* 1997, Klippel *et al.* 1997, Scheid *et al.* 2002). Akt kinase is involved in mechanisms of cell survival, growth and vascular remodeling. Gingras *et al.* (1998) and Kitamura *et al.* (1998) suggested that the activation of PI3K/Akt cascade plays an important role in protein synthesis involved in vascular remodeling and hypertrophy, although Akt kinase is a kinase of "cell survival", because of its antiapoptotic effect (Downward 1998, Zhuang *et al.* 2011). Mechanisms of AT $_1$ receptor-mediated PI3K-dependent activation of Akt kinase is not yet well understood, but it seems to play an important role in redox-sensitive signaling pathways and ROS-mediated c-Src activation (Thomas and Brugge 1997, Ushio-Fukai *et al.* 1999). c-Src is cytoplasmic tyrosine kinase, which is activated especially *via* superoxide anions generated by NADPH oxidase.

Another kinase cascades activated through Ang II are mitogen-activated protein kinase (MAPK) cascades which are universal signal transduction modules. MAPKs are activated through Ang II are ERK 1/2 (extracellular signal regulated kinase), JNK (c-Jun N-terminal kinase), p38, etc. (Robinson and Cobb 1997).

ERK 1/2 participates on regulation of expression of growth and differentiation factors. Mechanism of ERK activation is not yet completely explained. Activation starts through β and γ subunits of G protein and through receptor associated with tyrosine kinase Shc (Src homology domain) (Apostolidis and Weiss 1997, Berk and Corson 1997, Schieffer *et al.* 1997). Tyrosine kinase associated receptor stimulates joining p21ras receptor *via* a phosphorylation cascade. This receptor includes adaptor proteins with guanine nucleotide exchange factor. GDP/GTP exchange of p21ras protein is stimulated through Shc-Grb2-Sos (son-of-sevenless) complex. Grb2 (growth factor receptor-bound protein 2) is stimulated by autophosphorylation of tyrosine kinase receptor. Serine c-Raf kinase is linked to plasma membrane with p21ras protein. Serine c-Raf kinase phosphorylates MEK (MAPK/ERK kinase). MEK dually phosphorylates threonine and tyrosine residues in Thr-Glu-Tyr motive, resulting in ERK 1/2 activation (ERK 1: 44-kDa MAPK isoform; ERK 2: 42-kDa MAPK isoform) (Touyz and Schiffrin 2000). ERK 1/2 phosphorylation cascade plays a role in regulation of expression of growth and differentiation factors. *In vitro* studies suggested that PPAR γ activation can inhibit activation of ERK 1/2 induced by Ang II (Goetze *et al.* 1999, Takeda *et al.* 2000, Diep *et al.* 2002, Fukuda *et al.* 2002).

Effect of PPAR γ on oxidative stress and cell stress response regulated by Nrf2

Oxidative stress represents disruption of redox homeostasis for benefit of prooxidants, which exceed antioxidant capacity of cell, resulting in potential damage (Sies 2007). ROS produced in low concentration by different ROS sources in organism are an integral part of several intracellular signaling pathways during physiological processes (Touyz *et al.* 2003).

ROS are main contributors of oxidative stress in cells during physiological and pathological processes. The main enzyme sources of ROS include mitochondrial respiratory chain, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, xanthine oxidase and

uncoupled NO synthase. They are controlled under physiological conditions using cell stress detection of Nrf2 signaling pathway. This cellular protection system is activated in pathophysiologic condition during oxidative and electrophilic stress (Elahi *et al.* 2009, Rodrigo *et al.* 2011, Touyz and Briones 2011).

The Keap1/Nrf2/ARE is a complex system maintaining redox homeostasis in normal or stress conditions. These signaling pathways consist from Nrf2 protein/nuclear factor, Keap1 protein and ARE element (antioxidant response element) (Nguyen *et al.* 2009). The Keap1 protein regulates negatively Nrf2 activity through cysteine residues which are sensitive to presence of ROS (Kang *et al.* 2004). During oxidative stress Nrf2 can be released from connection with Keap1 and is translocated to the nucleus where induces transcription of genes by ARE (Hur *et al.* 2010, Tkachev *et al.* 2011). ARE is present within regulatory areas of several cytoprotective target genes directly involved in the production of antioxidant and detoxification proteins (Reichard *et al.* 2007, Gardlik *et al.* 2011, Majzunova *et al.* 2013).

Further production of detoxification and antioxidant proteins is involved in the elimination of reactive oxidants and electrophilic products. These processes are performed through conjugation reactions detoxifying of xenobiotics by production of enzymes in detoxification phase II (e.g. glutathione-S-transferase, NAD(P)H: quinone oxidoreductase 1), direct inactivation of ROS and increasing the antioxidant capacity of cells (e.g. catalase, superoxide dismutase, heme oxygenase-1) and regulation of glutathione production (e.g. glutamate-cysteine ligase) (Ishii *et al.* 2002, Gardlik *et al.* 2011, Hur and Gray 2011).

During chronic stress, some mechanisms appear to “switch off” Nrf2 activity. This process occurs after Nrf2 inactivation by aberrant phosphorylation by Fyn (fgr/yes novel protein) and GSK3 β (glycogen synthase kinase 3 β). GSK3 β phosphorylates Fyn which affected phosphorylation of Nrf2 in nucleus. This action results in the export of Nrf2 from the nucleus to the cytosol and binding to Keap1 with the subsequent degradation of Nrf2 (Jain and Jaiswal 2006, Kanninen *et al.* 2011).

Connection between PPAR γ and Nrf2

PPAR γ maintains redox homeostasis by activation and repression of several signaling pathways. In the case of Nrf2 there is a reciprocal transcriptional regulation between genes of Nrf2 and PPAR γ . Nrf2

contains putative PPREs and counter PPAR γ gene contain ARE (Park *et al.* 2004, Cho *et al.* 2010). Experiments with Nrf2 null mice show that expression of PPAR γ is reduced due to direct effect of Nrf2 lack. Nrf2 induces PPAR γ expression by binding to at least two ARE sequences in the upstream promoter region of the nuclear receptor (Huang *et al.* 2010, Cho *et al.* 2010). Furthermore, Nrf2 expression is weakened in mice with decreased PPAR γ (Park *et al.* 2004). A positive feedback loop between PPAR γ and Nrf2 probably exists, where PPAR γ may act directly or through upstream pathway for Nrf2 activation (Polvani *et al.* 2012). In addition, nuclear receptor PPAR γ and transcription factor Nrf2 may act synergically in the activation of antioxidant genes (Ishii *et al.* 2004, Park *et al.* 2004). ARE and PPRE response element coexist in GSTA2 promoter. GSTA2 gene encodes detoxification enzyme glutathione S-transferase A2, where ARE site is important in the transactivation of the GSTA2 gene by PPAR γ and RXR ligands for the full gene transactivation (Park *et al.* 2004). Similar expression of CD36 is dependent on both proteins, but transcription of CD36 may be induced independently by Nrf2 or PPAR γ , depending on the cellular context (Ishii *et al.* 2004).

There are another ways of activation and repression of antioxidant and prooxidant pathways. PPAR γ creates a heterodimer with RXR and together regulate gene transcription (Desvergne and Wahli 1999, Varga *et al.* 2011). As dimers, PPAR γ :RXR bind to PPRE located in the promoter region of target genes. PPAR γ may directly modulate the expression of several antioxidant and prooxidant genes in response to oxidative stress. It was observed that ligand-activated PPAR γ promotes the expression of manganese SOD (MnSOD) (Ding *et al.* 2007), GPx3 (Chung *et al.* 2009), the scavenger receptor CD36 (Ishii *et al.* 2004), heme oxygenase-1 (HO-1) (Kronke *et al.* 2007) and the mitochondrial uncoupling protein 2 (UCP2) (Chan *et al.* 2010), whereas it down-regulates COX-2 and iNOS (Zhao *et al.* 2006, Vandewalle *et al.* 2008, Polvani *et al.* 2012).

One mechanism of PPAR γ action represents the coexistence of PPREs and ARE in the same genes. The expression of scavenger receptor CD36 (mediates the recognition and internalization of oxidized lipids, antioxidant enzymes catalase, HO-1 and mitochondrial MnSOD are transcriptionally regulated through PPREs (Ishii *et al.* 2004, Ding *et al.* 2007, Kronke *et al.* 2007).

Redox homeostasis disruption in cardiovascular diseases and the role of PPAR γ

Disruption of redox homeostasis and pathophysiological ROS level leads to series of damage effects that participate in the development of cardiovascular diseases. Hypertension is a multifactorial complex disease leading to the damage of several organ systems. The factors participating in hypertension development include SNS activation, RAS up-regulation, altered G protein-associated signaling and inflammation (Touyz 2005, Harris *et al.* 2008). Oxidative stress is a common factor of these processes. It affects

processes participating in vascular remodeling, growth and proliferation of vascular smooth muscle cells, lipid peroxidation, extracellular matrix remodeling, fibrosis, monocyte invasion and inflammation. Moreover, increased ROS levels are associated with higher vascular contractility, vascular and cardiac fibrosis and remodeling, manifested by blood pressure elevation and cardiac output increase (Montezano and Touyz 2014).

Polvani *et al.* (2012) pointed out that nuclear receptor PPAR γ can affect redox homeostasis by interacting with signaling pathways, including nuclear factor Nrf2, NF- κ B, Wnt/ β -catenin and FOXO proteins (Fig. 3).

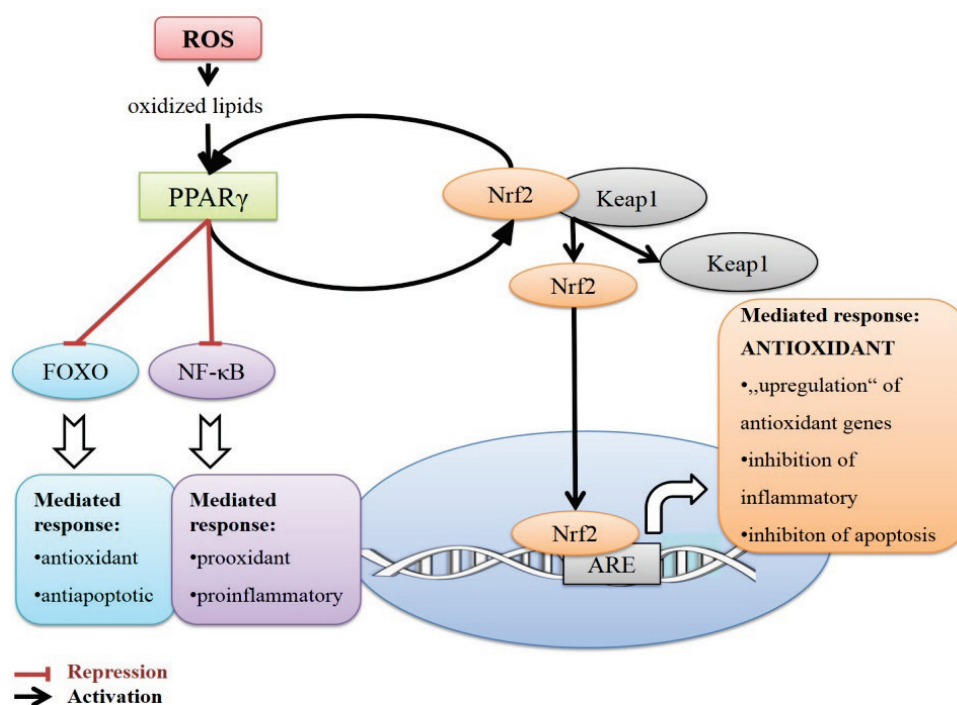


Fig. 3. Cross-talk of PPAR γ with other signaling pathways, such as nuclear factor Nrf2, NF- κ B, Wnt/ β -catenin, FOXO proteins in oxidative stress response (modified according to Polvani *et al.* 2012).

In the pathogenesis of hypertension it was observed that ROS overproduction in the central nervous system increases SNS activation in peripheral vessels (Peters *et al.* 2000, Nagao and Yamaguchi 2012). Furthermore, increased AT $_1$ receptor expression, almost localized on glutamatergic neurons in rostral ventrolateral medulla (RVLM), can modulate excitatory or inhibitory neurons and their postsynaptic activity (Hu *et al.* 2002). This can lead to higher SNS activity and positive correlation with BP (Dampney *et al.* 2007).

Moreover, ROS overproduction in the kidneys increases Ang II production and Ang II-mediated renal

vasoconstriction (Just *et al.* 2008), renin release (Welch *et al.* 1983), renal nervous activity (Lai *et al.* 2012) as well as the activation of endothelin-1 and thromboxane (Wang *et al.* 2004).

TZDs treatment decreases ROS production in vascular smooth muscle cells (Dobrian *et al.* 2004, Ceolotto *et al.* 2007) and endothelial cells (Dobrian *et al.* 2004, Sorrentino *et al.* 2007), allowing the decrease in blood pressure. Chan *et al.* (2010) suggest that RSG administration shows central antihypertensive effect. With respect to the central role of oxidative stress in neural mechanisms of hypertension development (Peters

et al. 2000, Kimura *et al.* 2005), the antihypertensive effect of RSG can be mediated through PPAR γ -dependent transcriptional up-regulation of antioxidant mechanisms in RVLM (Chan *et al.* 2010).

PPAR γ protects against the apoptosis of cardiomyocytes and glial cells from oxidative stress by induction of transcription of Bcl-2 (B-Cell CLL/Lymphoma 2) (Ren *et al.* 2009).

In humans vessels, the expression of HO-1 is induced in the presence of oxidative stress and high glucose level after TZDs administration (Wang *et al.* 2011). Oxidative stress in RVLM, where sympathetic premotor neurons reside, contributes to sympathoexcitation and hypertension. Metabolic syndrome, which is activated in rats by high-fructose diet, increases sympathetic vasomotor activity, blood pressure and ROS level, while it reduces NO and mitochondrial electron transport capacity. Treatment of these animals by TZDs (PIO) abrogated all those molecular events in this model of metabolic syndrome and ameliorated sympathoexcitation and hypertension (Wu *et al.* 2014).

Conclusions

The PPAR γ nuclear receptor is transactivated by its ligands and functions as an activator or repressor of a variety of signaling pathways. It may be also involved in insulin signaling regulation, RAS suppression, as well as in the regulation of antioxidant response, either directly or through the Nrf2 transcription factor.

PPAR γ regulates a number of homeostatic functions of the glucose and lipid metabolism and, as a nutrient-sensing signaling sensor, it can influence nutritional programming to hypertension and/or metabolic syndrome. Several ligands of this receptor can potentiate its activation. Many exogenous ligands such as thiazolidinediones: rosiglitazone, pioglitazone or tideglusib have a range of positive effects on cardiovascular diseases and the metabolic syndrome, however, some of them have harmful side effects. The usefulness and effectiveness of PPAR γ ligands on lifestyle-related diseases has yet to be established. Future investigations have to search for various endogenous ligands and their effects.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

(PP)1 – protein phosphatase 1
 15d-PGJ2 – 15-deoxy- Δ -12,14-prostaglandin J₂
 ACE – angiotensin converting enzyme
 AF-1 and AF-2 – activation function motive 1 and 2
 Akt – Akt serine/threonine kinase 1
 AMPK – AMP-activated protein kinase
 Ang 1-7 – angiotensin 1-7
 Ang I and Ang II – angiotensin I and II
 ARE – antioxidant response element
 AT₁ and AT₂ – angiotensin-receptor type1 and 2
 Bcl-2 – B-cell CLL/Lymphoma 2
 BMAL-1 – brain and muscle Arnt-like protein-1
 BP – blood pressure
 cAMP – cyclic adenosine 3', 5' monophosphate
 CD36 – cluster determinant 36
 COX-2 – cyclo-oxygenase 2
 c-Src – c-Src tyrosine kinase
 eNOS – endothelial nitric oxide synthase
 ERK 1/2 – extracellular signal regulated kinase
 ET-1 – endothelin 1
 FGF – fibroblast growth factor
 FOXO – forkhead box protein O
 Fyn – fgr/yes novel protein
 GC rich promoters regions – guanine and cytosine rich promoters regions
 GDP – guanosine diphosphate
 GLUT4 – glucose transporter type 4
 GPCR – G-protein-coupled receptors
 GPx3 – glutathione peroxidase 3
 Grb2 – growth factor receptor-bound protein 2
 GSK-3 β – glycogen synthase kinase-3beta
 GSTA – glutathione S-transferase A2
 GTP – guanosine-5'-triphosphate
 HO-1 – heme oxygenase-1
 iNOS – inducible nitric oxide synthase
 IR – insulin receptor
 IRS – insulin receptor substrate
 JNK – c-Jun N-terminal kinase
 Keap1 – Kelch-like ECH associated protein
 MAPK – mitogen-activated protein kinase
 Mas – Mas proto-oncogene, G protein-coupled receptor
 MEK – MAPK/ERK kinase
 NCoR – nuclear receptor corepressor
 NF- κ B – nuclear factor kappa B
 NO – nitric oxide
 Nox – NADPH oxidase
 Nrf2 – Nuclear factor E2-related factor 2
 PDK1 – 3' phosphoinositide-dependent kinase-1

PI3K – phosphatidylinositol-3-kinase	SHIP2 – Src homology 2 domain containing inositol 5-phosphatase 2
PIO – pioglitazone	SHR – spontaneously hypertensive rats
PIP2 – phosphatidylinositol 4,5-bisphosphate	SMRT – silencing mediator of retinoic acid and thyroid hormone receptor
PIP3 – phosphatidylinositol (3,4,5)-triphosphate	SMRT – silencing mediator of retinoic acid and thyroid hormone receptor
PKA, PKB and PKC – protein kinase A, B and C	SNS – sympathetic nervous system
PLC – phospholipase C	SOD – superoxide dismutase
PP2A – protein phosphatase 2A	Sos – son-of-sevenless
PPAR – peroxisome proliferator-activated receptor	Sp1 protein – specificity protein 1 transcription factor
PPRE – peroxisome proliferator response element	STAT – signal transducers and activators of transcription
RAF – Raf-1 proto-oncogene, serine/threonine kinase	SUMO – small ubiquitin-like modifier
RAS – renin-angiotensin system	TZDs – thiazolidinediones
ROS – reactive oxygen species	UCP2 – uncoupling protein 2
RSG – rosiglitazone	VSMC – vascular smooth muscle cells
RVLM – rostral ventrolateral medulla	Wnt – Wingless-type MMTV integration site
RXR – retinoid X receptor	
SH2 – src homology 2	
Shc – Src homology domain	

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