Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2013 April ; 33(4): 676–678. doi:10.1161/ATVBAHA.112.301125.

A Clinical Link Between PPARγ and the Renin-Angiotensin System

Curt D. Sigmund
Department of Pharmacology, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

Abstract

A mechanistic link between PPARγ and the renin-angiotensin system (RAS) has been previously proposed but clinical evidence supporting the relationship is incomplete. In the current issue of *Arteriosclerosis Thrombosis Vascular Biology*, Caron-Debarle et al. show that four patients with familial partial lipodystrophy associated with early-onset severe hypertension (FPLD3) carry mutations in PPARγ that impair its ability to act as a ligand-activated transcription factor. Cells isolated from these patients, and cells transfected with the same mutations in PPARγ exhibit activation of the cellular RAS, increased production of reactive oxygen species and markers of inflammation, all of which are dependent upon the angiotensin-II AT_1 receptor. This translational study further supports a role for PPARγ as a regulator of blood pressure through its ability to modulate the RAS.

Peroxisome proliferator-activated receptor γ (PPARγ) is a ligand activated transcription factor and target of the thiazolidinedione TZD class of anti-diabetes medications. PPARγ is best recognized for its role in adipogenesis but is also a regulator of systemic metabolism as evidenced by the pleiotropic abnormalities (lipodystrophy, insulin-resistance, and metabolic syndrome) caused by PPARγ mutations.[1-3] Clinical studies of TZD use in type 2 diabetes including the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) trial documented improved endothelial function and modest but significant reductions in blood pressure.[4] Some of the same mutations which cause lipodystrophy and diabetes also cause severe hypertension and preeclampsia in human patients,[3] and in knock-in mice.[5,6] Evidence suggests that PPARγ activity in the vascular endothelium and smooth muscle are important regulators of endothelial function, smooth muscle contraction, and systemic blood pressure.[7,8]

Data suggesting a role for PPARγ in regulating blood pressure led many to search for downstream mediators. Early studies suggested that activation of PPARγ might antagonize the renin-angiotensin system (RAS) by inhibiting expression of the angiotensin-II (Ang-II) AT_1 receptor (AT_1R) in vascular smooth muscle cells (vSMC).[9] PPARγ may also regulate expression of the renin and angiotensinogen (AGT) genes.[10,11] TZD administration to Ang-II treated Sprague-Dawley rats blunts the development of hypertension, endothelial dysfunction, and the induction of proinflammatory mediators.[12] Similarly, TZD treatment of hypertensive transgenic mice over-expressing the renin and AGT genes improved

Correspondence to: Curt D. Sigmund, PhD Roy J. Carver Chair of Hypertension Research Department of Pharmacology Roy J. and Lucille A. Carver College of Medicine University of Iowa Iowa City, Iowa, 52242 Phone: 319-335-7604 Fax: 319-353-5350 curt-sigmund@uiowa.edu.

endothelial function and lowered arterial pressure.[13] An association between PPARγ and the RAS was also suggested by Tsai *et al*. [5] (and reviewed in [14]) who reported that mice carrying a mutant PPARγ allele equivalent to the mutation which causes hypertension in humans, exhibited increased blood pressure and elevated expression of AGT and AT_1R in several adipose depots. That certain AT_1R blockers (ARB) exhibit partial PPARγ agonist activity suggests an unexpected yet physiologically uncertain link between PPARγ and the RAS.[15] What remained unclear is whether this association between PPARγ and the RAS is clinically relevant?

In the current issue of *Arteriosclerosis Thrombosis Vascular Biology*, Caron-Debarle *et al*.[16] explore this question in 4 members of 2 unrelated families with familial partial lipodystrophy associated with early-onset severe hypertension (FPLD3). Blood pressure control in these patients required aggressive treatment with multiple antihypertensive agents (including ARBs) concurrent with treatment for hyperlipidemia, and in 3 of the 4 subjects, diabetes. They identified two previously unreported mutations in PPARγ. R165T occurs in a highly conserved residue in the DNA binding domain, whereas L339X truncates the protein to lack a portion of the ligand binding domain. All 4 patients were heterozygous for one of the mutations. *In vitro* studies of cultured fibroblasts and peripheral blood mononuclear cells (PBMC) derived from the patients, as well as human vSMCs transfected with the PPARγ mutants revealed that the mutant and wildtype alleles were equivalently expressed, but the mutants lacked transactivation capability. Unlike other mutations in PPARγ which cause hypertension, they do not act dominant negatively and most likely cause haploinsufficiency.[3] TZD treatment improved glycemic control and eliminated the need for high dose insulin therapy in 2 subjects suggesting that the potential to activate the wildtype PPARγ allele was preserved. Although untested in the current study, it is possible that the activity of the wildtype PPARγ may have been impaired in these patients. Inflammation has been reported to impair PPARγ activity by CDK5-mediated phosphorylation, an effect prevented by TZDs.[17] Indeed, hypertension and diabetes are commonly associated with inflammation and fibroblasts isolated from these patients exhibited increased NFκB activity, markers of inflammation, and increased reactive oxygen species (ROS). AT_1R signaling is well known to cause inflammation and oxidative stress, and interestingly, expression of AT_1R, renin, and AGT were all markedly increased in patient fibroblasts and PBMCs, cells we do not immediately associate with the RAS. The increase in AT_1R expression occurred concomitantly with increased Ang-II-induced ERK phosphorylation, and AT_1R silencing prevented the induction of ROS and inflammation suggesting that some of the pathological consequences of the mutations may be mediated by AT_1R activation.

These data suggest a mechanism whereby impaired PPARγ activity induces AT_1R expression and signaling which promotes oxidative stress and inflammation. That the silencing of AT_1R in these cells also decreased expression of renin and AGT suggests their increase may be secondary to increased AT_1R signaling. We could therefore hypothesize the existence (at least in the isolated cells from these patients) of a feed-forward mechanism whereby elevated AT_1R action augments further Ang-II production which may then amplify the pathological response (see Figure). It is interesting to note that the induction of renin expression by AT_1R in fibroblasts and PBMCs is contrary to Ang-II-induced inhibition of renin expression in kidney. Unfortunately, information regarding the status of the systemic RAS in these patients before treatment was not available, whereas under therapy, 2 patients had normal plasma renin activity (PRA), plasma and urinary aldosterone, and potassium. Although the clinical relevance of the RAS in fibroblasts and PBMCs remains uncertain, AT_1R signaling in vSMC is of obvious importance in the regulation of vasomotor function. A feed-forward mechanism as described above could potentially induce endothelial dysfunction and smooth muscle contraction and exacerbate the hypertension.

Regardless of the many strengths of this translational study a number of important questions remain. First, did TZD treatment of the effected patients have an effect on arterial pressure; or in a more general sense, does PPARγ activation lower blood pressure in humans by antagonizing the RAS? We know that treatment of the patient fibroblasts with rosiglitazone, which presumably activated wildtype PPARγ decreased expression of the RAS genes, and blunted the increase in ROS, NFκB and IL-6 induced by the PPARγ mutations. Thus at the cellular level, a normal phenotype could be rescued by activation of wildtype PPARγ by TZD. Even with the declining clinical use of TZDs this may be important because new PPARγ activators, which do not act as full PPARγ agonists are in development. At least one of these new compounds prevents impairment of PPARγ activity by post-translational mechanisms induced by inflammation, and importantly, this compound may lack some of the detrimental side effects of TZDs.[18] It's effect on the cardiovascular system has yet to be explored. Second, is the AT_1R gene the primary PPARγ target gene or are their other PPARγ target genes in the relevant tissues which become dysregulated in response to mutant PPARγ? We recently reported that PPARγ induces expression of a target gene in the aorta which controls the activity of the Cullin-3 pathway, a regulator of RhoA/Rho kinase signaling and vasomotor function.[19] We also recently identified a physiological connection between PPARγ and AT_1R activity (but not AT_1R expression) in mesenteric resistance vessels through Regulator of G protein signaling 5 (RGS5), a novel PPARγ target gene that functions as a small GTPase-activating protein to regulate AT_1R signaling.[20] Third, are all the cardiovascular effects in these patients mediated by PPARγ and the RAS? This may be important to consider because there are other inherited lipodystrophies which are not caused by mutations in PPARγ yet are associated with hypertension.[21,22] A common feature of all these disorders is insulin resistance and a loss or redistribution of adipose tissue (e.g. loss of subcutaneous adipose with accumulation of abdominal adipose).[23] The mechanistic contributions of these features to hypertension in these patients remains unclear. Interestingly, as these patients often display evidence of inflammation (e.g. increased plasma C-reactive peptide) a role for impaired PPARγ activity and thus increased RAS activity should be considered.

In closing, there are other FPLD3 subjects that carry different mutations in PPARγ and exhibit a much broader array of neurologic and hematologic symptoms in addition to severe metabolic syndrome.[24] It is therefore likely that PPARγ has far reaching effects which may extend beyond the RAS. Studies of human patients and patient cells like Caron-Debarle *et al*.[16] combined with studies employing animal models will likely uncover other mechanistic links between PPARγ, the RAS, and other important pathways that may lead to effective therapies for the spectrum of disorders which encompass the metabolic syndrome.

Acknowledgments

Funding:

NIH grants HL048058, HL061446, HL062984, HL084207 to CDS. The author also gratefully acknowledges the generous research support of the Roy J. Carver Trust.

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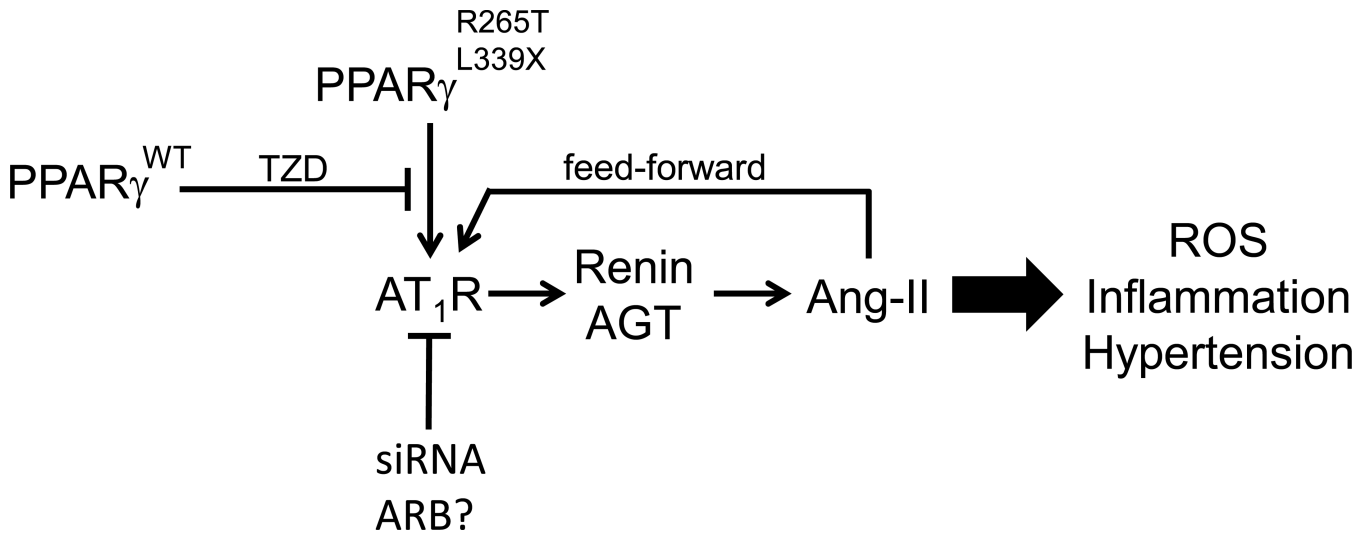

Figure. The PPARγ:RAS Relationship

Schematic showing that PPARγ mutations cause an increase in expression of the AT_1R which induces hypertension perhaps through ROS and inflammation. The increase in renin and AGT elevates production of Ang-II, which in cells from the effected patients, causes a feed-forward mechanism which may further increase AT_1R signaling. TZD treatment activates the wildtype PPARγ allele and blunts the effects of the mutation. A similar effect is attained by blocking AT_1R expression by an siRNA and presumably with an ARB.