



## Review

## Regulation of advanced glycation end product (AGE)-receptor (RAGE) system by PPAR-gamma agonists and its implication in cardiovascular disease

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## ABSTRACT

Non-enzymatic modification of proteins by reducing sugars leads to the formation of advanced glycation end products (AGEs), whose process has been reported to progress under physiological aging, oxidative stress or diabetic conditions. There is a growing body of evidence that AGEs and their receptor (RAGE) axis is involved in the pathogenesis of cardiovascular disease (CVD). Indeed, engagement of RAGE with AGEs is shown to elicit oxidative stress generation and subsequently evoke inflammatory and thrombotic responses in various types of cells, including endothelial cells, smooth muscle cells, macrophages and renal cells, thus playing an important role in the development and progression of vascular injury in both diabetes and non-diabetes. These observations suggest that the inhibition of AGE formation, down-regulation of RAGE expression or blockade of the RAGE downstream signaling may be a promising therapeutic target for preventing CVD. Recently, peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) is involved in not only adipocyte differentiation, but also vascular homeostasis. Therefore, in this study, we review effects of PPAR $\gamma$  agonists on the AGE–RAGE system and their implication in CVD.

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## 1. Introduction

Reactive derivatives from non-enzymatic glucose–protein condensation reactions, as well as lipids and nucleic acids exposed to reducing sugars, form a heterogeneous group of irreversible adducts called “advanced glycation end products (AGEs)” [1,2]. Since the formation and accumulation of AGEs are dependent on the turnover rate of the chemically modified target, the time available, and the sugar concentration, its process has been reported to progress under physiological aging or diabetes [3–6]. Under hyperglycemic, oxidative stress or inflammatory conditions, this process begins with the conversion of reversible Schiff base adducts to

more stable, covalently bound Amadori rearrangement products [3–6]. Over the course of days to weeks, these Amadori products undergo further rearrangement reactions to form the irreversibly bound moieties known as AGEs such as pentosidine, pyrraline and imidazolone [3–8]. Recent studies have shown that AGEs and their receptor (RAGE) axis is implicated in the pathogenesis of various devastating disorders such as diabetic vascular complications, cardiovascular disease (CVD), Alzheimer's disease, cancer growth and metastasis, insulin resistance and nonalcoholic fatty liver disease [9–17]. Indeed, engagement of RAGE with AGEs is reported to elicit oxidative stress generation and subsequently evoke inflammatory and thrombotic responses in various types of cells, including endothelial cells, smooth muscle cells, macrophages and renal cells, thus playing an important role in the development and progression of these devastating disorders. RAGE is a member of the immunoglobulin superfamily of cell surface molecules capable of

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interacting with a broad spectrum of ligands including a diverse group of reducing sugar complexes with proteins, lipids and nucleic acids [9,10]. V-domain of RAGE is supposed to interact with AGEs [18]. These observations suggest that the inhibition of AGE formation or AGE–RAGE interaction, down-regulation of RAGE expression or blockade of the RAGE downstream signaling may be a promising therapeutic target for preventing various life-threatening disorders such as CVD.

Peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) is a nuclear receptor protein [19–21]. It functions as a master transcriptional factor that promotes differentiation of preadipocytes by activating adipose-specific gene expression [19–21]. Recently, PPAR $\gamma$  activity has been shown to influence the gene expression involved in carbohydrate and lipid metabolism [19–21]. Indeed, pioglitazone and rosiglitazone, ligands for PPAR $\gamma$ , improve insulin resistance in diabetic patients, and now become one of the most popular anti-diabetic drugs in the developed countries [19–21]. Moreover, there is accumulating data that activators of PPAR $\gamma$  exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells [22–25]. These observations suggest that PPAR $\gamma$  agonists may have atheroprotective properties *in vivo* through its pleiotropic effects. However, as far as we know, there is no comprehensive review about the regulation by PPAR $\gamma$  agonists of the AGE–RAGE system. Therefore, in this study, we review the effects of PPAR $\gamma$  agonists on the AGE–RAGE system both *in vitro* and *in vivo* and their clinical implication in CVD.

## 2. Involvement of AGE–RAGE system in CVD

A variety of molecular mechanisms by which AGE–RAGE system contributes to the development and progression of CVD have been proposed [1,7–11,14]. AGEs formed on the extracellular matrix results in decreased elasticity of vasculatures, and quench nitric oxide (NO), which could mediate defective endothelium-dependent vasodilatation [26]. The AGE–RAGE-elicited oxidative stress inactivates NO to form peroxynitrite, which could further induce endothelial cell (EC) damage and platelet activation. AGE modification of low-density lipoprotein (LDL) exhibits impaired plasma clearance and contributes to increased LDL levels *in vivo*, thus being involved in atherosclerosis [27]. In addition, binding of AGEs to RAGE results in the generation of intracellular reactive oxygen species (ROS) generation and subsequent activation of the redox-sensitive transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) in vascular wall cells, which promotes the expression of a variety of atherosclerosis-related genes, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), tissue factor, vascular endothelial growth factor (VEGF), and RAGE [28–35]. Further, AGEs have the ability to induce osteoblastic differentiation of microvascular pericytes, which would contribute to the development of vascular calcification in accelerated atherosclerosis as well [36].

Smooth muscle cell (SMC) proliferation, migration, and neointimal expansion upon arterial injury were strikingly suppressed in homozygous RAGE null mice compared with those observed in wild-type littermates [37]. These data highlight key roles for RAGE in modulating SMC properties after injury and suggest that RAGE is a logical target for the suppression of untoward neointimal expansion consequent to arterial injury. In addition, administration of a recombinant soluble form of RAGE (sRAGE) consisting of the extracellular ligand-binding domain, has been recently shown to not only suppress the development of atherosclerosis but also to stabilize established atherosclerosis in diabetic apolipoprotein E-null mice [38,39]. The interaction of the rennin–angiotensin system (RAS) and the AGE–RAGE system in the development of and pro-

gression of CVD has also been proposed. The AGE–RAGE interaction augments angiotensin II-induced SMC proliferation and activation, thus being involved in the progression of atherosclerosis as well [40]. AGEs have been actually detected within atherosclerotic lesions in both extra and intracellular locations [41]. Furthermore, RAGE overexpression is associated with enhanced inflammatory reaction and matrix metalloproteinase (MMP) expression in plaque macrophages in diabetic patients [42]. Therefore, the AGE–RAGE interaction could contribute to plaque destabilization by inducing culprit MMP expression.

## 3. Involvement of AGE–RAGE system in chronic kidney disease (CKD)

In recent years, there is a growing body of evidence that even minor renal dysfunction is associated with high risks of cardiovascular events [43,44]. Now CKD is generally thought to be one of the risk factors for CVD [45].

The AGE–RAGE system is involved in the development and progression of CKD as well [46]. AGE formation on extracellular matrix proteins alters both matrix–matrix and cell–matrix interactions [46]. AGEs stimulate insulin-like growth factor-I, -II, platelet-derived growth factor, VEGF and transforming growth factor- $\beta$  (TGF- $\beta$ ) in mesangial cells, which in turn mediate production of type IV collagen, laminin and fibronectin [46,47]. AGEs induce TGF- $\beta$  overexpression in both podocytes and proximal tubular cells as well [48]. Recently, RAGE-overexpressing diabetic mice have been found to show progressive glomerulosclerosis with renal dysfunction, compared with diabetic littermates lacking the RAGE transgene [49]. Further, diabetic homozygous RAGE null mice failed to develop significantly increased mesangial matrix expansion or thickening of the glomerular basement membrane [50]. Taken together, these findings suggest that the activation of AGE–RAGE axis contributes to the expression of VEGF and enhanced attraction/activation of inflammatory cells in the diabetic glomerulus, thereby setting the stage for mesangial activation and TGF- $\beta$  production; processes which converge to cause albuminuria and glomerulosclerosis.

We have recently found that the AGE–RAGE-mediated ROS generation activates TGF- $\beta$ –Smad signaling and subsequently induces mesangial cell hypertrophy and fibronectin synthesis by autocrine production of angiotensin II [51]. This pathway may provide an important link between the AGE–RAGE axis and the RAS in promoting the development and progression of CKD.

## 4. Effects of PPAR $\gamma$ agonists on AGE formation

There are a couple of papers to show that PPAR $\gamma$  agonists could inhibit the formation of AGEs [52,53]. Indeed, Sobal et al. reported that the long-term glycation and glycoxidation of LDL as measured by 5-hydroxymethyl-2-furaldehyde formation and binding of fructosamine, was inhibited by troglitazone [52]. The inhibitory effects of PPAR $\gamma$  agonists on AGE formation may be ascribed to its anti-oxidative properties [22–25]. However, the clinical relevance of the AGE-lowering effects of PPAR $\gamma$  agonists is still unclear because troglitazone inhibits the activities of glyoxalase-I and -II, enzymes that detoxify methylglyoxal and other  $\alpha$ -oxo-aldehydes, which could result in the formation of AGEs [54].

## 5. Effects of PPAR $\gamma$ agonists on RAGE signaling pathways

Several papers have shown that PPAR $\gamma$  agonists block the deleterious effects of AGEs both in cell culture and animal model [55–65]. Activation of PPAR $\gamma$  by rosiglitazone inhibited AGE-induced inducible NO synthase expression, nitrite release, fibronectin and type IV collagen production by mesangial cells

[55,56]. Rosiglitazone attenuated the AGE-induced interleukin-8 and soluble ICAM-1 generation by proximal tubular epithelial cells as well through the suppression of signal transducer and activator of transcription [57]. Further, rosiglitazone was reported to inhibit renal extracellular matrix accumulation, fibronectin, type IV collagen and PAI-1 production and subsequently reduce proteinuria in AGE-injected rats [56]. Rosiglitazone also inhibited the AGE-induced proliferation, connective tissue growth factor (CTGF) overexpression and reduced NO production in cardiac fibroblasts [58].

Suppression of RAGE expression may be a molecular target of PPAR $\gamma$  agonists [59–66]. Marx et al. reported that the stimulation of human ECs with PPAR $\gamma$  agonists such as rosiglitazone and pioglitazone decreased basal as well as tumor necrosis factor- $\alpha$ -induced RAGE expression via suppression of NF- $\kappa$ B activation. They showed that PPAR $\gamma$  agonists decreased AGE- as well as  $\beta$ -amyloid-induced MCP-1 expression in ECs [59]. Wang et al. reported that rosiglitazone reduced RAGE expression and S100-induced SMC proliferation *in vitro* and suppressed neointimal formation after balloon angioplasty in both diabetic and non-diabetic rats [60]. Further, we have found that telmisartan, an angiotensin II type 1 receptor blocker (ARB), could down-regulate RAGE expression and suppress its downstream signalings in various cells through its unique PPAR $\gamma$ -modulating ability [61–65]. Indeed, telmisartan suppressed RAGE expression at both mRNA and protein levels in human cultured ECs, which were prevented by GW9662, an inhibitor of PPAR $\gamma$ . Telmisartan inhibited up-regulation of mRNA levels for MCP-1, ICAM-1, VEGF and PAI-1 in AGE-exposed ECs [61,62]. In addition, telmisartan also down-regulated RAGE mRNA levels and subsequently inhibited superoxide generation as well as MCP-1 expression in mesangial cells, all of which were prevented by GW9662 [63]. Since another ARB, candesartan, did not suppress the AGE-induced ROS generation in mesangial cells and that an anti-oxidant *N*-acetylcysteine inhibited MCP-1 production by AGE-exposed mesangial cells, telmisartan may inhibit the AGE-elicited MCP-1 expression in mesangial cells by blocking the RAGE-mediated superoxide generation via PPAR $\gamma$  activation. Moreover, we have recently found that telmisartan, but not candesartan, decreased the AGE-induced RAGE expression, ROS generation and subsequent C-reactive protein (CRP) expression in human hepatoma cells, Hep3B cells, all of which were blocked by GW9662 as well [64]. Telmisartan was also found to improve AGE-elicited insulin resistance in Hep3B cells by inhibiting serine phosphorylation of insulin receptor substrate-1, at least

in part, via activation of PPAR $\gamma$  [65]. Grape seed proanthocyanidin extracts also inhibited the AGE-induced VCAM-1 expression in ECs by suppressing RAGE expression via PPAR $\gamma$  activation [66]. Taken together, these observations suggest that PPAR $\gamma$  agonists reduce RAGE expression and subsequently block the downstream signaling pathways, thus limiting the cells' susceptibility toward pro-inflammatory, pro-thrombotic and insulin resistant effects of AGEs.

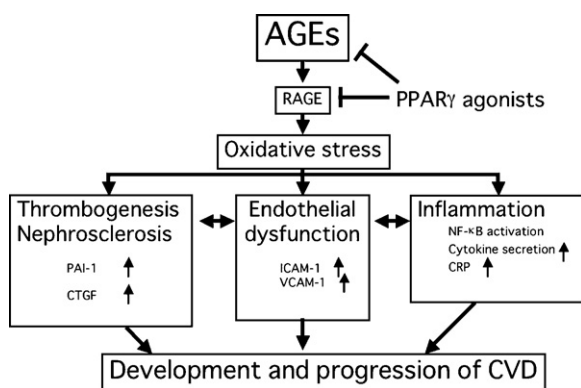
We posit an overall scheme concerning the protective role of PPAR $\gamma$  agonists in the AGE–RAGE system-involved cardiovascular disorders (Fig. 1).

## 6. Perspective: potential utility of PPAR $\gamma$ agonists on the AGE–RAGE-elicited cardiac dysfunction

Structural modification by AGEs of collagen in the arterial wall or heart might play important roles in arterial or cardiac elasticity. Indeed, aminoguanidine, an inhibitor of AGE formation, was shown to increase vascular elasticity, improve left ventricular–arterial coupling, and decrease vascular permeability in diabetic rats [67]. Further, aminoguanidine prevented the decreased myocardial compliance and cardiac hypertrophy in diabetic animals [68,69]. Diabetic homozygous RAGE null mice were protected from the adverse impact of ischemia/reperfusion injury in the heart as well [70]. In addition, treatment with ALT-711 (alagebrium), a cross-link breaker of AGEs, restored left ventricular collagen solubility and cardiac brain natriuretic peptide (BNP) in association with reduced cardiac AGE levels and abrogated the increase in RAGE, connective tissue growth factor, and collagen III expression [71]. A recent clinical trial has shown that patients who received ALT-711 experienced statistically significant reduction in arterial pulse pressure and an increase in large artery compliance in aged humans compared to patients who received placebo, thus suggesting that it may provide a novel therapeutic approach for this abnormality, which occurs with diabetes and isolated systolic hypertension [72]. Sixteen weeks of treatment with ALT-711 was found to result in a decrease in left ventricular mass and improvements in left ventricular diastolic filling and quality of life in patients with diastolic heart failure [73]. These observations suggest that AGE–RAGE system plays a central role in many of the alterations observed in the diabetic heart. Although there is no report to show the beneficial effects of PPAR $\gamma$  agonists on the AGE–RAGE-elicited cardiac dysfunction, the above-mentioned findings suggest the potential utility of PPAR $\gamma$  agonists in AGE–RAGE system-associated cardiac abnormalities. However, we should briefly discuss the adverse effects of PPAR $\gamma$  agonists on cardiovascular system. A recent meta-analysis of 42 clinical trials suggest that rosiglitazone is associated with the increased risk for myocardial infarction and death from CVD in diabetic patients, although there is still controversy about the findings [74]. Further, treatment with rosiglitazone or pioglitazone is reported to increase the risk for weight gain, peripheral edema and heart failure [75].

## 7. Conclusions

We reviewed here the pathological role of the AGE–RAGE system in cardiovascular and renal diseases in diabetes. The inhibition of the AGE–RAGE system by PPAR $\gamma$  agonists may be a promising therapeutic approach for CVD in human diabetes. However, unfortunately, there is no drug in the pipeline against the potential targets identified in this review. The development of the selective PPAR $\gamma$  modulator (SPPARM) without undesirable side effects [76] may be needed for the treatment of CVD in diabetes.



**Fig. 1.** Protective role of PPAR $\gamma$  agonists in the AGE–RAGE system-involved cardiovascular disorders. AGE–RAGE interaction induces oxidative stress generation in various types of cells, thus eliciting inflammation, endothelial dysfunction, thrombosis and nephrosclerosis via overexpression of a variety of adhesion molecules, cytokines and growth factors. PPAR $\gamma$  agonists not only inhibit the formation of AGEs, but also reduce RAGE expression, thereby playing a protective role against the AGE–RAGE system-involved cardiovascular disorders.

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