

Role of Peroxisome Proliferator Activator Receptor γ in Diabetic Retinopathy Pathophysiology

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Abstract

Diabetic retinopathy (DR) is one of the most common complications of diabetes and one of the leading causes of blindness worldwide. DR involves an abnormal pathology of major retinal cells, including retinal pigment epithelium, vascular cells (endothelial cells and pericytes), retinal microglial cells and retinal ganglion cells. The biochemical mechanisms associated with hyperglycemic-induced DR are through multifactorial processes. Peroxisome proliferator-activated receptor- γ (PPAR- γ) plays an important role in the pathogenesis of DR by inhibiting diabetes-induced retinal leukostasis and leakage. Despite DR causing eventual blindness, only a few visual or ophthalmic symptoms are observed until visual loss develops. Laser photocoagulation therapy is the most common treatment. However, this therapy may cause retinal damage and scarring. Therefore, early medical interventions and prevention are the current management strategies. The recent advancements in the knowledge of the pathogenic alterations driving ocular damage and vision loss in DR strongly focus on PPAR- γ as a valuable target to control high glucose-induced inflammation and apoptosis. This review provides an analysis of potential involvement of PPAR- γ in various mechanisms and pathways associated with progression of DR.

Keywords: Diabetic retinopathy; Peroxisome proliferator-activated receptor γ ; Neovascularization; Neuroretinal degeneration

Abbreviations: DR: Diabetic Retinopathy; PPAR- γ : Peroxisome Proliferator-Activated Receptor- γ ; AGEs: Advanced Glycation End products; 15-dPGJ₂: 15-deoxy- $\Delta^{12,14}$ -Prostaglandin J₂; NF- κ B: Nuclear Factor-kappaB; TNF- α : Tumor Necrotic Factor; COX-2: Cyclo-Oxygenase-2; ICAM-1: Intercellular Cell adhesion Molecule-1; VCAM-1: Vascular Cell Adhesion Molecule-1; MMP-9: Matrix Metalloproteinase-9; VEGF: Vascular Endothelial Growth Factor; iNOS: Inducible Nitric Oxide Synthase; BRB: Blood Retinal Barrier; NGF: Nerve Growth Factor

Introduction

Diabetic retinopathy (DR) is one of the most prevalent diabetic eye diseases. It is a vision-threatening disease presenting neurodegenerative features associated with extensive vascular changes [1,2]. The prevalence of DR increases with the duration of diabetes, and nearly all patients with type I diabetes and more than 60% with type II diabetes have some degree of retinopathy after 20 years [3-5]. Therefore, early detection and prevention are the current management strategies [6]. Chronic hyperglycemia is believed to be the primary pathogenic factor for inducing damage to retinal cells [7-9]. However, the mechanisms that lead to DR are not fully understood [10]. DR is characterised by increased vascular permeability, due to a breakdown in the blood retinal barrier (BRB), which causes macular edema, followed later by the development of vascular microaneurysms, hemorrhages, hard exudates and intraocular pathological neovascularization [11,4]. Moreover, degenerative changes, including increased apoptosis, glial cell activation, microglial activation, and altered glutamate metabolism, occur beyond the vascular cells of the retina [12]. Laser photocoagulation therapy is the most common treatment modality for DR. However, this therapy may damage neural tissue, resulting in the deterioration of vision [13]. Therefore, development of new therapeutic strategies for the treatment of excessive retinal vasopermeability, angiogenic changes and apoptosis of neurons are the basis for further research focus [12,14].

The Peroxisome Proliferator-Activated Receptor- γ (PPAR- γ) is a

ligand-activated nuclear receptor that belongs to the nuclear hormone receptor superfamily [15]. PPAR- γ plays an important role in glucose metabolism, angiogenesis, inflammation and neuroprotection [16,17]. Synthetic PPAR- γ ligands, the thiazolidinediones (TZDs), including pioglitazone and rosiglitazone improve insulin resistance in diabetic patients, and have become one of the most popular anti-diabetic drugs in developed countries [18-20]. In addition natural PPAR- γ ligands, such as 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15-dPGJ₂) have very potent anti-inflammatory effects that also modulate cellular defense against oxidative stress [21,22]. PPAR- γ agonists have been shown to inhibit endothelial dysfunction, neurotoxic inflammation and subsequently neurodegeneration, partially through the abilities of agonist bound PPAR-RXR heterodimers to antagonize the deleterious effects of advanced glycation end products and oxidative stress. This largely describes the consequences of Nuclear Factor-KappaB (NF- κ B) transcription factor inhibition, modulating the composition of the cellular membrane and down-regulation of protein inflammatory genes and cytokines [23-26]. Moreover, there is accumulating data to show that PPAR- γ activators exert anti-inflammatory, anti-oxidative and anti-proliferative effects in various cells including major retinal cells [16,27-30,9].

However, very limited research has been undertaken on PPAR- γ ligands in the modulation of DR related pathophysiology. Thus,

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this review presents a detailed discussion summarising potential involvement of PPAR- γ ligands in various mechanisms and pathways associated with modulation of DR-related pathogenesis.

Diabetic Retinopathy

Diabetes damages all the major cells of the retina, vascular cells (endothelial cells and pericytes) [31,32], pigment epithelial cells [33], retinal microglial cells and retinal ganglion cells [16,34]. Basement membrane thickening, pericyte drop out and retinal capillary non-perfusion occur prior to the damage, which changes the production pattern of a number of mediators, such as growth factors, vasoactive agents, coagulation factors and adhesion molecules. These result in increased blood flow and capillary diameter, proliferation of the extracellular matrix and thickening of basal membranes, altered cell turnover (apoptosis, proliferation, hypertrophy) and procoagulant/proaggrenant patterns, and finally angiogenesis with tissue remodeling. These pathological changes cause increased retinal vasopermeability and breakdown of the BRB, resulting in retinal hemorrhage, swelling, exudates, and retinal detachment [6,35,36]. DR has many elements that suggest chronic neurodegeneration, including neural apoptosis, loss of ganglion cell bodies, reduction in thickness of the inner retina, glial reactivity, neurofilament abnormality, slowing of optic nerve retrograde transport, changes in electrophysiological activity, and resultant deficits in perception [37]. Moreover, neuroretinal degeneration initiates and/or activates several metabolic and signaling pathways as well as in the disruption of the BRB [38].

The underlying pathophysiological mechanisms associated with hyperglycemia-induced diabetic retinopathy are through excessive formation of advanced glycation end products (AGEs) and production of excessive oxidative stress [39,6]. Moreover, these biochemical mechanisms lead to a cascade of events, such as promotion of apoptosis, inflammation, neurodegeneration and angiogenesis, which induce damage to diabetic retina, leading to DR [39,12,6] (Figure 1).

AGEs in diabetic retinopathy

AGEs are associated with modification of proteins or lipids that

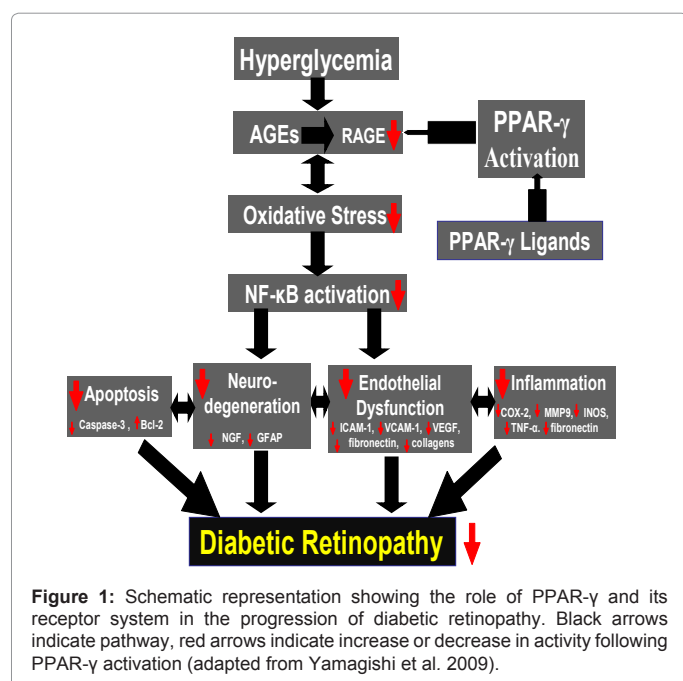


Figure 1: Schematic representation showing the role of PPAR- γ and its receptor system in the progression of diabetic retinopathy. Black arrows indicate pathway, red arrows indicate increase or decrease in activity following PPAR- γ activation (adapted from Yamagishi et al. 2009).

are generated from intermediate glycation products by non-enzymatic reaction of glucose with protein side chains [40,41]. These intermediate glycation products undergo further condensation, dehydration or rearrangement, leading to eventual irreversible AGEs formation [42]. AGEs formation occurs normally over time whereas an accelerated rate of AGE formation is accompanied by hyperglycemia [43]. The accumulated AGEs products are detected in the neural retina and vascular cells of diabetic animals, responsible for mediating the pathological angiogenesis and hyper-permeability in retina [44,45]. Several bodies of evidence suggest that the interaction between AGEs and their receptor (RAGE) activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and enhances the formation of oxygen radicals, with subsequent activation and translocation of NF- κ B, followed by release of pro-inflammatory cytokines and growth factors [39]. Moreover, AGEs can provide the early molecular pathogenesis mechanisms responsible for neuronal apoptosis and neuro-glial reaction [46]. In addition, AGEs enhance apoptosis in retinal pericytes, corneal endothelial cells, neuronal cells and renal mesangial cells through increased oxidative stress or via induced expression of pro-apoptotic cytokines [47-49]. Indeed, AGEs induce apoptosis, angiogenesis, breakdown of the BRB, and leukocyte adhesion in the retina. Thus, AGEs are detrimental to the retinal vasculature and contribute to the pathogenesis of DR [50,51].

Oxidative stress in diabetic retinopathy

Oxidative stress appears when there is a serious imbalance between generation of reactive oxygen species (ROS) and its clearance by anti-oxidant defenses [52,53]. Activation of RAGEs results in production of oxidative stress (conversely, glycation itself is promoted by oxidative stress), and subsequent activation of NF- κ B transcription factor in micro-vascular endothelial cells that are considered to be linked to endothelial dysfunction [54,55]. Retina, a tissue rich in polyunsaturated fatty acid, uses more oxygen and glucose oxidation than any other tissue in the body, and is very susceptible to damage [56]. Diabetic induced-oxidative stress, followed by activation of NF- κ B in the retina, is early events in the pathogenesis of DR [57-60]. Moreover, oxidative stress has been linked to the accelerated apoptosis of retinal ganglion cells, retinal capillary cells and micro-vascular abnormalities in DR [61,62].

NF- κ B in Diabetic Retinopathy

NF- κ B is a multi-protein complex which can activate many kinds of genes involved in cellular functions. Pathogenic stimuli allow NF- κ B to enter the nucleus, and to bind to DNA recognition sites in regulatory regions of target genes [63-65]. NF- κ B is required for maximal transcription of many pro-inflammatory molecules thought to be important in the generation of inflammation, including cell interaction molecules (eg intracellular adhesion molecule 1), critical enzymes (eg inducible nitric oxidase synthase, cyclooxygenase-2), and a number of cytokines (eg interleukin-1 β , tumor necrosis factor- α , IL-6) [24,66]. The activation of NF- κ B is considered a key signaling pathway by which high glucose induces apoptosis in endothelial cells [67]. In the retina, NF- κ B is localised in sub-retinal membranes and in micro-vessels [44] and its activation is considered responsible for the accelerated loss of pericytes observed in DR [68]. Moreover, the study has shown that diabetes-induced capillary degeneration, observed in DR, is at least closely associated with NF- κ B activation in both vascular and neural compartments of retina and subsequent inflammatory response [69].

Inflammation in diabetic retinopathy

In recent years inflammation has been linked to vascular leakage

in DR, at least in part [70,71]. Hyperglycemia is a contributing risk factor for the development of vascular dysfunction and production of inflammatory markers [72,73]. Indeed, pro-inflammatory cytokines, chemokines and other inflammatory mediators play an important role in the pathogenesis of DR. These lead to persistent low-grade inflammation, which in turn leads to neuronal cell death, the adhesion of leukocytes to the retinal vasculature (leukostasis), breakdown of BRB and tissue ischemia [74-77]. Several inflammatory molecules are involved in the pathogenesis of DR, including tumor necrotic factor (TNF- α), fibronectin, cyclo-oxygenase-2 (COX-2), intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and matrix metalloproteinase-9 (MMP-9) [76-79].

Angiogenesis in diabetic retinopathy

Angiogenesis is defined as the growth of new vessels from pre-existing capillaries, which is a complex process comprising endothelial cell proliferation, migration, extracellular proteolysis, tube formation and vessel remodeling [80]. In retina, vascular endothelial growth factor (VEGF) is the major angiogenic factor for neovascularization and vascular leakage via the mitogen-activated protein kinase (MAPK) pathway [81-83]. Additional pro-angiogenic factors, including MMP-9, are also required for the process of ocular neovascularization through either synergistic effects with angiogenic factor or as a stimulant for the secretion of angiogenic factors [84]. In addition, MMP-9 expression acts as a factor in increasing vascular permeability in ocular neovascularization [85]. Neurotrophic factor, such as nerve growth factor (NGF), alone or in combination with other biological active endogenous molecules, have been found to exert angiogenic activity *in vitro* and *in vivo* [86,87]. Moreover, NGF has been shown to induce neuronal-driven angiogenesis, leading to pathologic retinopathy [88].

Apoptosis in diabetic retinopathy

Apoptosis is programmed cell death and is characterised by chromatin condensation, fragmentation, and formation of apoptotic bodies that can be triggered by various signals [89-91]. Retinal microvascular cells are lost selectively via apoptosis before other histopathology is detectable in diabetes [92,93,32]. As oxidative stress is closely linked to apoptosis in diabetes, oxidative stress-induced apoptotic episodes have been demonstrated by retinal abnormalities, potential visual changes and the onset of the first neural and vascular change [75,57,94]. Moreover, apoptotic cell death in retinal regions is a probable stimulus for the increased expression of molecules that enhance the breakdown of the BRB and lead to vascular proliferation [95,96]. Several studies have shown that retinal pigment epithelial cells, Glial cells [97], retinal ganglion cells [98] and retinal pericytes [89,99] undergo high glucose induced-apoptosis. The studies have shown that diabetes causes a chronic loss of neurons from the inner retina by increasing the frequency of apoptosis [100,101]. Moreover, it has been well established that apoptosis represents a final common pathway of cell loss and hence vision loss [102]. In addition, high glucose causes activation of several proteins involved in apoptotic cell death, including members of the caspase and Bcl-2 family [61]. Therefore, apoptosis plays an important role in the progression and pathogenesis of DR [61,89].

Neurodegeneration in diabetic retinopathy

Neurodegeneration is recognised as a pivotal feature of many diseases of the central nervous system. Although much of the research effort has focused on vascular changes, it is becoming apparent that the degenerative changes occur beyond the vascular cells of the retina.

These include apoptosis, glial cell reactivity, microglial activation, and altered glutamate metabolism [12]. Moreover, early neuronal and glial alterations are also evident in diabetes, including decrease in components of the electroretinogram [103] and increased apoptosis of retinal neurons [104]. Indeed, current evidences has shown that neurodegeneration of the retina is a critical component of DR [12]. In addition, early in the course of DR, Müller cells markedly up-regulate their expression of glial fibrillary acidic protein (GFAP) [105]. Retinal ganglion cells are the earliest cells affected and have the highest rate of apoptosis. Moreover, neuroretinal degeneration initiates and/or activates several metabolic and signaling pathways which participate in the microangiographic process as well as the disruption of the BRB [38]. Elevated levels of glutamate, the major excitatory neurotransmitter in the retina, have been found in experimental models of diabetes [106].

Pathogenesis of microglial cells in diabetic retinopathy

Retinal glial cells, including macroglia (Müller cells and astrocytes) and microglia, are considered channels of communication between retinal blood vessels and neurons owing to their special spatial arrangement and regulatory functions. Under normal conditions, microglia are characterised by a down-regulated phenotype when compared to other macrophage populations of peripheral tissues [15]. The maintenance of microglia in the "inhibited" state is crucial for the maintaining tissue homeostasis and preventing the destructive potential of inflammatory response [107]. Moreover, microglial activation appears early in the course of DR, before the onset of overt neuronal cell death [108]. In diabetes, retinal microglial cells are activated to release inflammatory cytokines, such as IL-1 β , TNF- α , NO, MMPs and VEGF, and excitatory amino acids, such as glutamate that initiate neuronal loss and BRB breakdown seen in DR [34,109]. The study has shown that in STZ-induced diabetic rats treated with minocycline, a semi-synthetic tetracycline that counteracts microglial activation, as well as decreasing the expression of pro-inflammatory cytokines, caspase-3 levels are also decreased, suggesting a potential neuroprotective anti-apoptotic effect of inhibition of microglial activation [108,15]. Moreover, in mice with alloxan-induced diabetes, changes in microglial cell morphology were the first detectable cellular modifications, apparently preceding ganglion cell apoptosis and increase in BRB permeability [110].

Pathogenesis of ganglion cells in diabetic retinopathy

Although the clinically demonstrable changes to the retinal vasculature in diabetes have led to the general assumption that the retinopathy is solely a microvascular disease, diabetes also damages non-vascular cells of the retina, resulting in loss of ganglion cells [62]. Numerous studies have suggested that exposure to AGEs, inflammation or oxidative stress might contribute to retinal ganglion cell apoptosis [62]. Moreover, the diabetes-induced degeneration of retinal ganglion has been shown to involve inhibiting the activation of the pro-inflammatory NF- κ B [69]. Another potential cause of retinal ganglion cell loss is excitotoxicity due to excessive synaptic glutamate activity [111]. Immunohistochemical studies of cross-sections of human retinas demonstrated an increase in expression of Bax, caspase-3 and caspase-9 in retinal ganglion cells from diabetic patients, suggesting at least some retinal ganglion cells might die via apoptosis [112]. Moreover, activated microglial cells in hypoxic neonatal retina produce increased amounts of pro-inflammatory cytokines, including TNF- α and IL-1 β that could induce retinal ganglion cell death [113].

Pathogenesis of retinal pigment epithelium in diabetic retinopathy

The retinal pigment epithelial (RPE) cells form a monolayer

between the neuroretina and the choriocapillaris which are the essential components of the outer BRB that maintain physiological and structural balance within the retina [114,115]. The main characteristics of RPE cells are the presence of tight junctions at the apical side of their lateral molecules, which limit access of blood components to the retina. Moreover, RPE and photoreceptors are particularly susceptible to oxidative stress because of high oxygen consumption by photoreceptors [116]. In response to damage caused by the hyperglycemic condition, RPE cells migrate and proliferate, leading to a break-down in adhesion between the RPE and the choroidal capillaries, followed by BRB breakdown compromising blood flow within the RPE layer and leading to eventual retinal edema [117]. These cascade episodes trigger the serum components and inflammatory cells to enter the vitreous cavity and sub-retinal space, exposing the RPE cells to a variety of cytokines, pro-inflammatory mediators, extracellular matrix proteins and growth factors, causing DR [118]. Several studies have shown that the expression of angiogenic cytokines, growth factors (e.g. VEGF) and metalloproteinases (e.g. MMP-9) are produced by RPE [119]. Moreover, the combined effects from chronic sustained inflammation and ROS generation promotes the development of RPE damage [120-122].

PPAR- γ and Diabetic Retinopathy

PPAR- γ is heterogeneously expressed in the mammalian eye, prominently present in the retinal pigmented epithelium, photoreceptor outer segments, choriocapillaries, and retinal ganglion cells [16,85,123]. Recent studies have shown that retinal expression of PPAR- γ was suppressed in experimental models of diabetes and in endothelial cells treated with high glucose [73]. Moreover, PPAR- γ ligands are potent inhibitors of corneal angiogenesis and neovascularization [124,125]. Administration of 15d-PG₂ inhibited VEGF-stimulated angiogenesis in rat cornea [125]. Similarly, choroidal neovascularization was markedly reduced by intravitreal injection of troglitazone. Laser photocoagulation-induced lesions in rat and monkey eyes showed significantly less leakage in troglitazone-treated animals [123]. In neonatal mice, intravitreal injection of rosiglitazone or troglitazone inhibited development of new retinal vessels. In the same study, TZDs have been found to inhibit retinal endothelial cell proliferation, migration, and tube formation in response to VEGF treatment [126]. In addition, rosiglitazone inhibits both the retinal leukostasis and retinal leakage observed in experimental diabetic rats, which leads to the aggravation of retinal leukostasis, and retinal leakage in diabetic mice [124]. Moreover, rosiglitazone has been shown to delay the onset of DR [127]. As inflammation plays a role in several neurodegenerative diseases, numerous research has been conducted on the role of PPAR- γ in inflammation-induced neurodegeneration [128-130]. Moreover, it has more recently become appreciated that PPAR- γ agonists act on neurons and microglia to inhibit neurotoxic inflammation and subsequently neurodegeneration, partially through the abilities of agonist bound PPAR-RXR heterodimers to antagonise NF- κ B mediated gene transcription of several inflammatory mediators such as COX-2 and iNOS *in vitro* and *in vivo* [23,131-133]. Troglitazone has been shown to prevent neuronal death induced by glutamate toxicity *in vitro* [134]. Similarly, retinal ganglion cells were rescued from death by troglitazone [16]. Therefore, the anti-inflammatory, anti-oxidative stress properties of PPAR- γ activation may allow the neuroprotection seen with PPAR- γ agonism [135]. These findings suggest that PPAR- γ is involved in the pathogenesis of DR (Figure 1).

PPAR- γ and AGEs

PPAR- γ ligands have a significant role in prevention of AGEs-

induced micro-vascular complications, including DR [136,137]. Indeed, PPAR- γ ligands have shown to inhibit the formation of AGEs [138,139]. The inhibitory action of PPAR- γ ligands on AGE formation may be ascribed to their anti-oxidative properties [27-30]. The study has shown that rosiglitazone inhibits extracellular matrix accumulation, fibronectin and type IV collagen in AGE-injected rats, and also inhibits the AGE-induced proliferation and NO production in cardiac fibroblasts [140,141]. Moreover, activation of PPAR- γ by rosiglitazone inhibits AGE-induced inducible NO synthase expression, nitrite release, fibronectin and type IV collagen production [142,141].

PPAR- γ in NF- κ B, inflammatory mediators and angiogenesis

PPAR- γ plays an important role in a variety of biological processes, including inflammation and angiogenesis, mediated through the inhibition of NF- κ B [143-146]. Rosiglitazone was shown to inhibit both retinal leukostasis and retinal leakage by the inhibition of NF- κ B activation, with consequent suppression of ICAM-1 expression [124]. In addition, recent evidence has shown that the suppression of PPAR- γ in diabetic retina is associated with the activation of NF- κ B target gene expression [147,73]. Stimulation of a pro-inflammatory response in microglia *in vitro* and the resulting production of neurotoxic inflammatory mediators were found to be suppressed by administration of a number structurally distinct PPAR- γ agonists [25,133]. In addition, TZDs have been shown to attenuate lipopolysaccharide-induced neuroinflammation by PPAR- γ activation in neural cells [25]. The activation of PPAR- γ inhibits the pro-inflammatory pathways, including cytokine secretion [148,149] and iNOS expression [150,151] in a variety of cell lines. Indeed, PPAR- γ agonists have been shown to suppress cytokine evoked neuronal iNOS expression, thereby preventing NO-mediated cell death of neurons [152]. Inhibition of ICAM-1 expression and retinal vascular leakage in experimental diabetes has been shown by rosiglitazone, and the increase in the same parameters by depletion of the gene encoding PPAR- γ [124]. PPAR- γ ligands have also been shown to inhibit the expression of VEGF receptors and the subsequent activation of downstream signaling pathways [153,125]. Moreover, rosiglitazone has been shown to inhibit retinal neovascularization in OIR by a mechanism downstream from VEGF-induced angiogenesis [153]. In addition, it has been suggested that ICAM-1 is involved in VEGF-induced leukocyte-endothelial cell interactions and subsequent (BRB) breakdown in the diabetic retina [154]. Furthermore, PPAR- γ activation inhibits VEGF-mediated angiogenesis through the modulation of the stimulated COX-2 expression and activity [155].

PPAR- γ and apoptosis

Apoptosis is a complex process, involving a multitude of signaling pathways that regulate the activities of pro- and anti-apoptotic members of the Bcl-2 family of proteins which play an important role in various cell types [156-158]. Oxidative stress can induce mitochondrial dysfunction, followed by cytochrome c release and subsequent activation of caspases, a group of enzymes that execute apoptosis [159,160]. A recent study has shown that rosiglitazone protects against oxidative stress-induced apoptosis through up-regulation of anti-apoptotic Bcl-2 family proteins [161]. Moreover, rosiglitazone and PPAR- γ over-expression protect against apoptosis induced by oxygen and glucose deprivation followed by re-oxygenation and up-regulation of Bcl-2 [162]. In contrast, down-regulation of NF- κ B activation by PPAR- γ ligands protects the cells from destruction via the apoptotic pathways [163,164]. A screen of FDA-approved compounds identified rosiglitazone as a novel anti-apoptotic agent in

retinal cells both *in vivo* and *in vitro* [102]. Troglitazone has shown cytoprotective activity in apoptotic-induced ARPE-19 cells [165]. One further study has indicated that 15d-PG₂ helps RPE cells to maintain mitochondrial integrity by prevention of cytochrome c release and subsequent activation of the apoptosis pathway [166,167]. Moreover, rosiglitazone has been shown to protect hippocampal and dorsal root ganglion neurons against A β -induced mitochondrial damage and NGF deprivation-induced apoptosis [168].

PPAR- γ in retinal microglia and retinal ganglion cells

The beneficial effects of PPAR- γ ligands on the ocular system have been supported by various reports. Troglitazone and 15d-PG₂ have been shown to protect retinal ganglion cells, RGC-5, from glutamate-induced apoptosis [16].

Microglial cells have shown to express PPAR- γ and that such basal expression is increased by its specific agonists, while it is reduced in the presence of microglial activators such as lipopolysaccharide (LPS) and interferon- γ (IFN- γ) [169]. Moreover, 15d-PG₂ has been shown to prevent LPS-induced iNOS expression and TNF- α production in primary microglial cultures, by mechanisms involving PPAR- γ activation and reduced activation of NF- κ B, which is known to mediate LPS and IFN- γ signaling [23]. Similarly, PPAR- γ agonists have been shown to modulate LPS-induced neuronal death in mixed cortical neurons, suggesting a PPAR- γ mediated mechanism of neuroprotection [132].

PPAR- γ and RPE cells

A number of studies have shown that RPE might be the prime target for oxidative stress and PPAR- γ ligands modulate cellular defense against the oxidative stress [170]. 15-dPG₂ protects RPE cells from oxidative stress by elevating GSH and enhancing MAPK activation through a PPAR- γ independent pathway [171]. In addition, 15-dPG₂, independent of its PPAR γ activity, protects RPE cells from oxidative injury by raising intracellular GSH levels and extending hydrogen peroxide-induced activation of Jun N-terminal kinase (JNK) and p38, suggesting the possible application of the agents in preventing ocular diseases from oxidative stress [172,171].

Conclusion

Diabetic retinopathy remains one of the major risk factors and a leading cause of preventable blindness worldwide. There is strong body of evidences on the prevalence of the variety of anti-angiogenic agents, anti-inflammatory agents, anti-oxidants, anti-fibrogenesis and neuroprotective agents present in the retinal regions for slowing down the progression of DR. Moreover, the increasing importance of understanding the specific molecular and biochemical changes in DR leads to the requirement for development of novel therapeutic interventions. Although it is an important cause of blindness, initially DR presents few visual or ophthalmic symptoms until complete visual loss occurs [4]. Current treatments of DR rarely improve visual function and are limited to surgical options in an advanced stage, with excessive side effects and significant financial burden. Hence, emerging treatments, possibly in combination with standard therapy, may provide superior efficacy and safety profile for the treatment or prevention of DR. Moreover, the new strategies move a paradigm in treating the early stages of DR. The recent advancements in the knowledge of the pathogenic alterations driving ocular damage and vision loss in DR strongly focus on PPAR- γ as a valuable target to control high glucose-induced inflammation and apoptosis. PPAR- γ functions as a transcription factor and thereby controls cellular processes at the

level of gene expression, through modulation by its nuclear receptor activity of selective downstream gene expression [173]. This review confirms PPAR- γ has potential involvement in various mechanisms and pathways associated with progression of DR. Moreover, PPAR- γ is an attractive and relatively unexploited therapeutic target in DR. However, the complexity of PPAR- γ activation not only provides beneficial effects but also introduces risks from undesirable side effects, such as cardiovascular complications with long term application [174]. Therefore, future studies are warranted for extensive investigation to gather proof of efficacy in various preclinical and clinical settings.

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