PPARα and Ocular Dieseases

Subjects: Others

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Mounting evidence suggests that peroxisome proliferator-activator receptor alpha (PPARα) activation can be a therapeutic target for various ocular diseases including diabetic retinopathy (DR). Here we describe functions of PPARα in the eye contributing to ocular homeostasis.

diabetic retinopathy PPARα SPPARMα HIF-1α

1. Introduction

Diabetic retinopathy (DR) is a complication of diabetes that affects the eyes in subjects with type 1 or type 2 diabetes mellitus [1]. DR develops because of a chronic abnormality of glycemic control [2]. In detail, DR progresses from an initial stage where high blood glucose levels damage the microvasculature [3]. Then, microvascular irregularities including hemorrhage, ischemia, and microaneurysms bring retinal neovascularization [3]. Abnormal vasculatures by retinal neovascularization lead to severe hypoxic conditions in the retina of the eye [3]. At the final stage, fibrovascular proliferation resulting in tractional retinal detachment by chronic severe hypoxic conditions causes vision loss [3]. However, recent evidence indicates that pathogenesis of DR contains far more complex mechanisms that are the involvement of multiple interlinked alterations via impairment of crosstalk between retinal neurons, glial cells, and vasculatures [4][5][6][7]. Emerging studies have demonstrated that neurons and glial cells in the central nervous system act as oxygen sensors and vascular regulators to interact with vascular cells for neurovascular homeostasis [8], and impairment of their crosstalk damages neurovascular homeostasis [8][9]. Although exact mechanisms have not been completely defined, possible major factors such as mitochondrial oxidative stress, inflammation, production of advanced glycation end products (AGEs), and activation of the protein kinase C (PKC) pathway have been proposed (along with the traditional concept of retinal neovascularization by hyperglycemia-induced microvascular irregularities) for the comprehensive pathogenesis of DR [10][11].

PPARα is from a nuclear receptor PPAR family (PPARα, PPARδ, and PPARγ), which regulates expressions of several genes affecting lipid and carbohydrate metabolism [12]. PPARα is named based on its ability to be activated by peroxisome proliferator chemicals, and it is the first member to be cloned among the PPAR isotypes [13]. PPARα is expressed in various types of cells in the skeletal muscle, heart, liver, brown adipose, kidney, intestinal mucosa, adrenal gland, eye, and most cell types present in the vasculature including endothelial cells, smooth muscle cells, monocytes, and macrophages [14][15][16][17][18][19][20][21]. PPARα activation was found to increase circulating levels of high-density lipoprotein cholesterol and decrease serum levels of triglycerides, free fatty acids and apolipoprotein, which improves an overall serum lipid profile and finally exerts positive effects on inflammation and insulin resistance [22][23][24]. Increasing evidence suggests that PPARα activation can be a strong therapeutic target for

various types of diseases such as cardiovascular diseases [25], dyslipidemia [26], and diabetes and its complications including DR [22]. However, its molecular mechanisms are far from being elucidated. In this paper, we review the therapeutic effects of PPARα agonists as a promising approach for the treatment of DR.

2. Functions of PPARα in the Eye

Experimental evidence indicates that PPARα is expressed in various tissues in diabetic microvascular diseases—the retina as well as kidney and nerve [20][21]. PPARα has been spotlighted as its expression levels decreased in the retinas with diabetes [27][28]. Decreased PPARα expression has been found to contribute to retinal inflammation and neovascularization, and pharmacological activation of PPARα has been shown to exert therapeutic effects against various ocular degenerative disorders [28][29][30]. A previous study showed that more severe retinal acellular capillary formation and pericyte dropout were observed in PPARα$^{-/-}$ mice with diabetes, compared with those in diabetic wild-type mice [29]. Another study demonstrated that retinal neurodegeneration was exacerbated in PPARα$^{-/-}$ mice with diabetes in comparison with that in diabetic wild-type mice [31]. Multiple proteomics data indicated that several oxidative stress markers such as *Gstm1* (glutathione-s-transferase m1), *Prdx6* (peroxidase 6) and *Txnrd1* (thioredoxin reductase 1) increased in diabetic retinas and that there were further increases in diabetic PPARα$^{-/-}$ retinas [31]. This implies that oxidative stress may become worsened by PPARα ablation in DR. PPARα activation increased retinal NADH (nicotinamide adenine dinucleotide + hydrogen) oxidation in diabetic mice, and treatment of fenofibric acid, an active metabolite of fenofibrate, reduced mitochondrial oxidative stress and cell death in retinal neuronal cell lines under 4-hydroxynonenal (4-HNE)-induced oxidative stress conditions [31]. This implies mitochondrial dysfunction by oxidative stress could be restored by PPARα activation.

In terms of an ischemic model other than the diabetic model, PPARα$^{-/-}$ mice with a laser-induced choroidal neovascularization (CNV) developed more severe CNV compared with wild-type CNV mice [32]. PPARα$^{-/-}$ mice with oxygen-induced retinopathy (OIR) also showed deleterious effects (such as increased retinal cell death and glial activation) in comparison with wild-type OIR mice [33]. Overexpression of PPARα using an adenovirus system attenuated increased endothelial progenitor cell circulation in OIR mice through inhibition of the hypoxia-inducible factor (HIF)-1α pathway, and mouse brain endothelial cells from PPARα$^{-/-}$ mice showed prominent activation of HIF-1α induced by hypoxia, compared with wild-type mouse brain endothelial cells [34]. This suggests anti-angiogenic effects of PPARα via HIF-1α inhibition, a novel protective molecular mechanism against retinal ischemic conditions.

Pharmacological PPARα activation by palmitoylethanolamide (PEA) reduced retinal neovascularization and fibrotic changes and suppressed glial activation in proliferative retinopathy and neovascular age-related macular degeneration mouse models [35]. In cardiovascular studies, PEA exerted direct vaso-relaxation of the bovine ophthalmic artery by using PPARα transcription factors, which suggests a role of PPARα on physiological vascular regulation [36]. This vaso-relaxing effect could increase supply of oxygen to the retina and prevent ischemic lesions, as observed in patients with ocular hypertension [37]. Another study demonstrated that administration of PEA showed enhancement of aqueous humor outflow facility and this effect appeared to be mediated partially by the

involvement of PPARα [38]. Those studies imply PPARα modulation could also be a promising therapeutic target for glaucoma [39].

Even though there are not many reports available on roles of PPARα in the ocular surface, recent evidence suggests that PPARα may play a critical role in regulation of inflammatory processes in the ocular surface [40]. Fenofibrate ameliorated a severity of ocular surface squamous metaplasia, commonly seen in patients with long-term deficiency of tear film [41] and suppressed formation of tear film instability via inhibition of macrophages and downregulation of pro-inflammatory factors [40]. In the corneal epithelium of mice with dry eyes by sleep deprivation, downregulation in PPARα expression was detected [42], and fenofibrate increased PPARα expression in cultured corneal epithelium sheets and restored a microvilli morphology [42]. This implies PPARα activation could have potential for use as a preventive agent in patients with a high risk of the dry eye. Other cornea studies indicated therapeutic roles of PPARα agonists against corneal inflammation and neovascularization [43][44]. Corneal neovascularization is closely related to a reduction in corneal transparency which is important for a visual acuity [45][46]. In rat corneal alkali burn models, corneal neovascularization was seen and a topical injection of fenofibrate suppressed its neovascularization through upregulation of PPARα mRNA expression and suppression of *Il-6*, *Il-1β*, *Vegf* and *Ang-2* mRNA expressions [43][44].

The above, taken together as accumulating evidence, supports the concept that it may be important to restore or boost PPARα expression for prevention of various ocular diseases. However, studies on downstream signaling effector molecules regarding PPARα activation need to be further unraveled.

3. Selective PPARα modulatorα (SPPARMα)

Pemafibrate is a novel selective PPARα modulator (SPPARMα) and has higher potency and selectivity for the activation of PPARα than other PPARα agonists, especially fenofibrate [43][47][48][49]. Several studies have shown that pemafibrate has therapeutic effects on retinal diseases [50][51][52]. One report showed that oral administration of pemafibrate increased plasma fibroblast growth factor 21 (FGF21) levels in OIR and inhibited retinal neovascularization through inhibition of HIF-1α and *Vegf* expressions [51]. In addition, long-acting FGF21 inhibited HIF activity in a photoreceptor cell line under hypoxic conditions [51]. Another report demonstrated oral administration of pemafibrate increased serum FGF21 levels in a streptozotocin-induced diabetic mouse model and preserved retinal function through maintaining synaptophysin expression, which regulates synaptic vesicle endocytosis [50]. Additionally, long-acting FGF21 directly upregulated synaptophysin expression in differentiated neurons in vitro [50]. The other study reported that pemafibrate directly inhibited diabetes-induced vascular leukostasis and leakage in the rat retina through upregulation of *THBD* expression which encodes the glycoprotein thrombomodulin [52], and indicated that pemafibrate can increase thrombomodulin expression in human umbilical vein endothelial cells and human retinal microvascular endothelial cells in vitro [52]. Even though further studies are required to elucidate various mechanisms, pemafibrate could offer retinal protection through upregulation of blood FGF21 levels to work on the damaged retina with suppression of pathological neovascularization, maintenance of retinal function, modulation of systemic metabolisms such as triglyceride or blood glucose levels, or a direct

increase in thrombomodulin expression in retinal endothelial cells to work on the damaged retina with suppression of vascular leakage, leukostasis and inflammation.

4. Conclusions

Diabetes mellitus is a complex metabolic disorder which is associated with insulin resistance, insulin signaling impairment, β-cell dysfunction, abnormal glucose and lipid metabolisms, inflammation and mitochondrial oxidative stress [53]. Likewise, development of DR has multiple interlinked alterations via dysfunctions of various cell types with enormous complex pathological mechanisms. Its development in turn cannot be prevented or protected by one therapeutic molecular target. Fortunately, PPARα targeting could be an alternative therapy to other present therapeutic agents in that it covers systemic enhancement of glucose and lipid metabolisms, anti-inflammation and anti-oxidative stress. Moreover, PPARα activation could ameliorate development of DR at an early stage through prevention of retinal vascular leakage[54][50][51]. This summary enables comprehensive understandings of protective roles of PPARα agonists against DR development. It can be useful for future studies on the protective effects of PPARα agonists against DR.

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