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Aldo-Keto Reductases: Multifunctional Proteins as Therapeutic Targets in Diabetes and Inflammatory Disease

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Abstract

Aldose reductase (AR) is an NADPH-dependent aldo-keto reductase that has been shown to be involved in the pathogenesis of several blinding diseases such as uveitis, diabetic retinopathy (DR) and cataract. However, possible mechanisms linking the action of AR to these diseases are not well understood. As DR and cataract are among the leading causes of blindness in the world, there is an urgent need to explore therapeutic strategies to prevent or delay their onset. Studies with AR inhibitors and gene-targeted mice have demonstrated that the action of AR is also linked to cancer onset and progression. In this review we examine possible mechanisms that relate AR to molecular signaling cascades and thus explain why AR inhibition is an effective strategy against colon cancer as well as diseases of the eye such as uveitis, cataract, and retinopathy.

Keywords

aldose reductase; inflammation; diabetes; cancer; inhibitor; cataract; retinopathy; nephropathy; neuropathy

1 Introduction

Aldo-keto reductases (AKRs) are a superfamily of enzymes involved in phase 1 metabolism of carbonyl substrates such as sugars, lipid aldehydes, keto-steroids and keto-prostaglandins [1–4]. The AKR superfamily contains 16 families (AKR1–16) [5] based on their high sequence similarity and common protein fold structure [AKR website: http://www.med.upenn.edu/akr/]. Enzymes within this family share many catalytic and structural properties. As a group, AKRs are nicotinamide adenine dinucleotide (phosphate) (NAD(P)H)-dependent oxidoreductases and are expressed as 34–37 kDa polypeptides [6].

The AKR family 1 includes: AKR1A (aldehyde reductases) [7], AKR1B (aldose reductases) [8], AKR1C (hydroxysteroid dehydrogenases) [9], AKR1D (steroid 5β-reductases) [9], and

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AKR1E (1,5-anhydro-D-fructose reductase) [10]. Among enzymes in the AKR family 1, AKR1B is the most well-studied with well over 6,000 reports published in PubMed (as of September 2016). Three AKR1B subfamily enzymes include AKR1B1 (human aldose reductase, HAR), AKR1B10 (human small intestine-like aldose reductase, HSIR) and AKR1B15 that are all encoded by genes localized to chromosome 7 [11] see Table 1. Since it is so well-studied among aldo-keto reductases, this review will focus primarily on recent studies on the role of aldose reductase (AR, AKR1B1) in human health, cancer, and ocular disease.

2 Function of AR in cellular responses

2.1 Inflammation

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor that controls gene expression affecting cellular processes such as cell cycle regulation, apoptosis [12], and activation of genes involved with inflammation [13]. In unstimulated cells, NF-κB is localized mainly in the cytoplasm [14]. Following cellular activation, NF-κB translocates into the nucleus and becomes acetylated by histone acetyltransferase (HATs) including CREB-binding protein (CBP) or its homolog p300 [15, 16]. Studies have shown that acetylation enhances both DNA-binding ability and transcriptional activity of NF-κB [17]. Removal of acetyl groups, catalyzed by a family of deacetylating proteins, can also influence the activity of transcription factors. SIRT1 (silent mating type information regulation 2 homolog) 1, the sirtuin 1 protein in mammals, is an NAD^+-dependent deacetylase that has been known to inhibit NF-κB transcription signaling by removing acetylation from its subunit RelA/p65 at lysine 310 [18]. Therefore, activity of SIRT1 plays a crucial role in regulating inflammatory responses by influencing the acetylation, and thus the activation state of NF-κB, the key transcription factor controlling expression of proinflammatory genes.

Pioneering studies by Ramana and Srivastava and their colleagues demonstrated a possible connection between AR and NF-κB activation when they showed that ARIs suppress the endotoxin-induced activation of NF-κB in macrophages [19]. Ramana and Srivastava have studied the intersection of AR and NF-κB by focusing on the role of AR in the NADPH-dependent detoxification of reactive aldehydes [20, 21]. AR has been shown to play a role in the reduction of toxic aldehydes such as 4-hydroxy-*trans*-2-nonenal (HNE) and its glutathione adducts (GS-HNE). Under oxidative stress conditions characterized by increased levels of lipid peroxidation, AR converts HNE and GS-NHE to 1,4-dihydroxynonene (DHN) and GS-DHN, respectively [22]. GS-DHN is the predominant metabolite derived from HNE due to the high reactivity of the aldehyde with glutathione. GS-DHN is a potent activator of the phospholipase C (PLC)/protein kinase C (PKC)/NF-κB pathway [23, 24]. Therefore, several studies indicated that AR can play an important role in the activation of the PLC/PKC/NF-κB cascade: AR inhibition suppresses these signaling events [23, 25–27]. In ocular models of endotoxin-induced uveitis, injection of LPS induces NF-κB activation in the anterior or posterior chambers of the eye [28, 29]. Clinically, topical corticosteroids, which act by suppressing NF-κB signaling [30], represent the primary treatment strategy for patients with noninfectious anterior uveitis [31, 32].

2.2 Intersection of glucose metabolism and inflammatory signaling

Hyperacetylation of NF-κB is well known to drive expression of inflammatory signaling genes [33]. Among many factors, high glucose has been shown to cause increased acetylation of NF-κB [34]. We hypothesize that the polyol pathway may provide a functional link between glucose metabolism, protein acetylation, and NF-κB activation. In the first step of the polyol pathway, AR catalyzes the NADPH-dependent conversion of glucose to sorbitol, which is then converted to fructose by the NAD^+-dependent sorbitol dehydrogenase (SDH) [35]. Thus, accelerated glucose flux through the polyol pathway results in a reduction in the NAD^+/NADH. Consequently, lower levels of NAD^+ could be expected to attenuate the NAD^+-dependent deacetylase activity of sirtuin-1 (Sirt-1), resulting in higher levels of NF-κB acetylation and therefore higher activity of Sirt-1 as an activator of inflammatory gene transcription. Thus, the imbalance between NAD^+/NADH provides a plausible linkage between polyol pathway activation and accumulation of acetyl-NF-κB, leading to an inflammatory phenotype (Fig. 1). We hypothesize that blockade of the poylol pathway by inhibition of either AR or SDH would prevent the high glucose-induced redox imbalance and thereby support the higher deacetylase activity of sirtulin 1. This would result in reduced levels of activated NF-κB and thereby lower expression of inflammatory genes.

Our studies are in concordance with those mentioned previously by Ramana and Srivastava [36–38], demonstrating that AR inhibition prevents endotoxin-induced inflammation in the eye [39, 40]. However, further studies will be needed to elucidate whether AR inhibition protects against the inflammatory response through its control of lipid derived aldehydes or alternatively through its influence on NAD^+/NADH ratios and acetylation status of transcription factors such as NF-κB. It is also possible that AR is involved in the inflammatory response via both pathways.

2.3 Oxidative stress

Hyperglycemia is a leading cause of oxidative stress in diabetic organs such as heart, kidney and eye. Pathways of hyperglycemia-induced oxidative stress include polyol pathway, mitochondrial electron transport system, protein kinase C (PKC) and advanced glycation end products (AGEs) (Fig. 2) [23]. During hyperglycemia, increased flux of AR-mediated reduction of glucose into sorbitol in a NADPH-dependent reaction was observed [41, 42]. NADPH plays reductive roles in metabolic steps, such as detoxification of reactive oxygen species (ROS) by the glutathione reductase/glutathione peroxidase system [43]. Therefore, excessive utilization of NADPH by the polyol pathway could compromise the ability of cells to protect themselves from oxidative stress.

In the secondary part of the polyol pathway, sorbitol is converted to fructose by SDH resulting in decreased ratio of NAD^+/NADH. Elevation of cytosolic NADH/ NAD^+ ratio leads to induction of ROS via mitochondrial NADH dependent pathway [44]. Increased NADH could also enhance the synthesis of diacylglycerol (DAG), which activates PKC and subsequently induces oxidative stress via PKC-dependent activation of NAD(P)H oxidase [45].

In addition to pyridine cofactor imbalances, AGEs resulting from hyperglycemia also contribute to oxidative stress [46]. AGEs are formed by nonenzymatic glycation reactions involving addition of a carbohydrate to a protein under high glucose conditions typical of diabetic individuals [46]. A study using glucose and fructose in comparison of the ability of forming AGEs showed that fructose forms AGE-BSA much faster than glucose [47]. This observation indicates that elevation of fructose from increased flux of the polyol pathway is another contributor for oxidative stress. Collectively, reduction of the ratio of NADPH/$NADP^+$ and NAD^+/NADH, and induction of AGEs are the major causes of oxidative stress in hyperglycemic environment (Fig. 3).

3 AR and Complications of Diabetes and Chronic Hyperglycemia

Many studies indicate that AR is implicated in inflammatory responses in immune cells [36–40], in heart [48], in kidney [49, 50] and in the eye [39, 51–53]. Additionally, AR is a major factor that causes a variety of diabetic complications such as autonomic neuropathy [54–58], ischemic myocardial injury [59–68] cardiomyopathy [48, 69, 70], nephropathy [71–73], cataract [74–79] and retinopathy [80–84] see Table 2. Pharmacological inhibition of AR or genetic deficiency in animal models with targeted disruption of the AR gene (AR knock out) brings about protection against these complications of diabetes and therefore provide a valuable tool for investigating pathogenesis caused by endotoxin or diabetic hyperglycemia. In this review, we will focus on AR inhibitors' effects on the major complications of diabetes mellitus.

3.1 Heart

3.1.1 Myocardial ischemic injury—Myocardial ischemia is a heart disease caused by lack of oxygen to cardiac muscle, usually due to blockage of blood vessels. Diabetic patients have high incidence of cardiovascular disease and myocardial infarction [85, 86]. In diabetic patients, more sorbitol accumulation and a decrease of NADPH, from a flux of AR, have been considered a causal factor in cardiac dysfunction [56, 87]. Many AR inhibitors such as Zopolrestat [59–61, 64], Tolrestat [63, 67] and Sorbinil [63, 67] have been reported effectively against myocardial ischemic injury in mice [64], rat [59, 60, 67] and rabbit [61, 63] models in both diabetic and non-diabetic conditions. To further understand the influence of AR in the heart, Ramasamy [62] and Bhatnagar [66] groups conducted experiments to measure AR activity and kinetic properties between normal and ischemic heart. They both found that ischemia increases myocardial AR activity, with higher *Kcat* and *Vmax* due to oxidative stress, without affecting *Km* [62]. In addition, the expression and activity of AR was significantly higher in aged hearts than young ones in a rat model [68]. Treating aged rats with AR inhibitor reduced ischemic injury and improved cardiac function in aged hearts [68]. Therefore, there is still a need for developing AR inhibitors on myocardial ischemia therapy.

3.1.2 Cardiomyopathy—Cardiomyopathy is degeneration of the myocardium, which causes severe cardiac failure and arrhythmia [88]. Studies showed that AR activation induces oxidative stress [39, 80] which could further trigger the NF-κB pathway [36, 38, 48]. The NF-κB pathway is involved in inflammatory condition which contributes to cardiovascular

dysfunction [89]. Sakamoto and Sugamoto observed the upregulation of AR-like gene in heart of cardiomyopathic rodent [70]. Ramana and colleagues also reported that AR inhibition is capable of preventing endotoxin-induced cardiomyopathy [48]. In addition, AR inhibition is able to prevent acute hyperglycemia-induced cardiac contractile dysfunction by reducing oxidative stress [69]. Taken together, observations above indicate that blockade of NF-κB pathway and oxidative stress through AR suppression could be a therapeutic strategy for preventing cardiomyopathy.

3.2 Kidney

3.2.1 Nephropathy—Diabetes has high influences in kidney complications and approximately 30% of diabetic patients have diabetic nephropathy, which is a leading cause of kidney failure in US [90, 91]. A strong immunohistochemical staining of AR was found in diabetic individuals, when compared to non-diabetic individuals, indicating that the level of AR is increased in the kidney of diabetics [92]. Supportive studies reported that high glucose in blood or cultured condition induces AR expression that leads to renal sorbitol accumulation [93–95], reactive oxygen species (ROS) production [96, 97] and inflammation [96] in nephropathy kidney or renal cells culture. Thus, a variety of AR inhibitors had been utilized for treating nephropathy by inhibiting the polyol pathway [73] but showed no influences on kidney weight, body weight or blood glucose [72]. In vivo studies utilizing AR null mice showed that genetic ablation of AR plays a strong protective role in preventing diabetic nephropathy [71]; however, the AR deletion in kidney came with abnormal functioning of the inner medulla [98]. Kidneys from diabetic patients also highly express TGF-β [99], which is an inducer of epithelial-mesenchymal-transition (EMT) [100]. Evidence from human mesangial cells showed that AR inhibition prevents transforming growth factor-beta 1 (TGF-β1)-induced fibronectin expression [101], which is an EMT marker that leads to kidney fibrosis. Another study conducted in renal proximal tubular cells showed that AR inhibition attenuated hyperglycemia-induced fibronectin elevation [93]. Collectively, AR inhibition could be a therapeutic strategy by preventing ROS production and EMT marker expression in patients of nephropathy.

3.2.2 Acute kidney injury—Acute kidney injury (AKI), also called acute renal failure (ARF), is a rapid onset loss of kidney function that may arise from an intense inflammatory process. In AKI mouse model, endotoxin injection increases the levels of blood urea nitrogen, creatinine and cytokines which cause vacuolar degeneration, apoptosis of renal tubular cells and immune cells infiltration [50]. Pretreatment with Fidarestat, an ARI, was able to ameliorate LPS-induced AKI by reducing inflammation and increase survival rate [49, 50]. The polyol pathway has recently been implicated in ischemia/reperfusion tissue injury. Hindlimb ischemia in mice revealed accumulation of sorbitol and fructose in ischemic muscles accompanying secretion of TNF-α and IL-6 in serum, which led to AKI [49]. Treatment with the AR inhibitor was effective at suppressing inflammatory reactions and renal failure [49]. These results suggest that AR inhibition may be a potential therapeutic strategy for treatment of AKI.

3.3 Peripheral Nervous System Disorders

3.3.1 Diabetic peripheral neuropathy—Diabetic peripheral neuropathy (DPN) is nerve damage that affects the 50% of patients with both Type 1 and Type 2 diabetes [102] and causes loss of sensation in the arms, hands, legs and feet [103]. DPN is considered one of the most painful complications affecting diabetic patients [104]. Patients usually feel painful prickling, burning, electrical, sharp, or jabbing sensation [105]. Assessing sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) allows clinicians to determine the degree of neuronal activity or damage [106]. Measurement of F-wave latency is the most common procedure to be diagnose peripheral neuropathy [107]. The efficacy of treatment on DPN is determined by using electrophysiological measurements of three key nerves—median motor, tibial motor, and median sensory nerves. A variety of strategies have been explored for management of DPN including the use of oriental medicine and natural products [108]. Conventional treatments of DPN include the commonly known analgesic drug such as non-steroidal anti-inflammatory drugs (NSAIDs) and opiates [109, 110]. Among the medicine in the management of DPN, tramadol is often used as a second-line analgesic. Tramadol is a semisynthetic opium-derived compound that binds to μ and δ opioid receptors and interferes the re-uptake of serotonin and norepinephrine [111, 112]. However, clinical use of tramadol is not recommended due to the high risk of epileptic seizures and psychiatric disorders. Other analgesic, in particular opium-derived, also has revealed physical and psychological side effects [113]. Therefore, alternative medicine is still an urgent need for management of DPN. Many natural compounds have been reported in the management of DPN. These compounds include phenolic compounds [114], cannabinoids [115, 116], vanilloids [117, 118] and essential fatty acid [119].

In the diabetic patient, AR is overexpressed in a variety of organs/tissues, particular in peripheral nerve [92], suggesting a possible link between AR and DPN. Sorbitol is the metabolite of glucose converted by AR in polyol pathway. Oka and Kato reported that increased accumulation of sorbitol results in the decrease of *myo*-inositol in the peripheral nerve [120]. Downregulatoin of *myo*-inositol subsequcetly results in lower Na^+, K^+ -ATPase activity, which is important for nerve conduction [120]. Therefore, blocking sorbitol accumulation by inhibiting AR polyol pathway is a strategy being considered for DPN treatment. Genetic studies support this concept, as AR knockout mice appear to be protected from delayed motor nerve conduction velocity [71]. Pharmacological inhibition of AR also showed encouraging or convincing results for clinical use. Epalrestat has been approved for use in the treatment of diabetic neuropathy in Japan [121]. Several clinical trials with epalrestat showed that 150 mg/day improves MNCV and SNCV, and subjective symptoms in patients with DPN [122, 123]. Two additional AR inhibitors, Fidarestat [124–126] and Rainrestat [124, 127, 128], also provide encouraging experimental and/or clinincal results in treatment of DPN and diabetic sensorimotor polyneuropathy (DSP), respectively. With these promising results of AR inhibitors, more about their efficacy and safety will need to be investigated to promote them in the U.S. market. Therefore, the natural products with lower cytotoxicity are potential candidates in AR inhibitor development for DPN treatment.

3.3.2 Cardiac autonomic neuropathy—Cardiac autonomic neuropathy (CAN) is characterized by dysfunction in the cardiac autonomic nerves causing dysregulation of heart rate. CAN results in higher incidence of heart failure and sudden death in diabetic patients [129]. In diabetic animal models, sorbitol accumulation from polyol pathway has been considered a major contributor to diabetic neuropathy [130]. Since it is considered an effective AR inhibitor, Sorbinil was used as a therapeutic agent in diabetic patients exhibiting improvement in CAN symptoms [54–56]. Other AR inhibitors such as Epalrestat [131–133], Ponalrestat [134–136] and Tolrestat [137, 138] were also reported as therapeutic agents against CAN. In 1981, Kline et al. developed a useful method entitled I-123 Meta-Iodobenzylguanidin (MIBG) to facilitate imaging the myocardium. This method provides quantitative information of heart rate [139] and is a useful tool in investigating diabetic autonomic disorder in patients [139]. Using MIBG, AR inhibition was observed to alleviate CAN progression in diabetic rats [57] and patients [58]. As a result, AR inhibitors might be a promising treatment for CAN. Thus, development of novel, effective, and nontoxic AR inhibitors is still necessary for slowing the progression of diabetic autonomic neuropathy [140].

3.4 Ocular Disorders

3.4.1 Uveitis—Uveitis is an ocular inflammatory disease of the uvea, the middle layer of the eye that consists of the iris (anterior uveitis), ciliary body (intermediate uveitis) and choroid (posterior uveitis), that contributes about 10 to 20% legal blindness per year [82]. Therefore, the aim of uveitis treatment is to prevent inflammatory responses. Topical eye drops or oral administration of glucocorticoid steroids is the most common treatment for uveitis [141]. In animal studies, lipopolysaccharide (LPS) is commonly used for induction of experimental uveitis, or so-called endotoxin-induced uveitis (EIU) [39, 51, 52, 142, 143]. LPS injection results in induction of TNF-α [51, 52, 142], ROS [51, 142], cyclooxygenase-2 (COX-2) [51, 52, 143], inducible nitric oxide synthase (iNOS) [51, 52, 143] and NF-κB activation [51, 143] in rodent eyes. Experimental autoimmune uveoretinitis (EAU) is another model for the investigation of ocular inflammatory response [52, 144]. Within these two uveitis models, secretion of proinflammatory cytokines is thought to play an important role resulting in damage to ocular tissue [52, 142]. Regarding the effects of AR on inflammatory responses, many studies using macrophages demonstrated that pharmacological inhibition or genetic ablation of AR attenuates LPS-induced cytokines secretion, oxidative stress and cell migration by suppressing MMP-9 and NF-κB activation [36–40]. In addition, studies also reported that downregulation of AR by enzymatic activity or gene expression is capable of preventing experimental models of EIU or EAU [39, 51, 52]. In the eye, retinal microglia (RMG) are one of the major immune cells that participate in surveillance in retinal environment. While they are typically located in the inner and outer plexiform layers in a healthy condition [145, 146], in uveitis they become activated [147] leading to morphological transformation [142] and migration into the outer nuclear layer (photoreceptor layer) where they secrete cytokines and peroxynitrites [144, 146]. In vitro studies using primary cells showed that RMG can be activated by LPS exposure [40, 148] and such activation can be suppressed by addition of an AR inhibitor or in mice lacking the functional allele of the AR gene [40]. For these reasons, we propose that AR could be a therapeutic target for uveitis.

3.4.2 Diabetic cataract—In 2010, it was estimated that around 285 million people worldwide had diabetes [149]. There is an estimation that around 552 million people, which is one in ten, will have diabetes by 2030 [150]. Many studies have shown that diabetes is associated with higher prevalence of cataracts, which remains a major cause of blindness in the world [151–153]. Tight glycemic control is known to reduce the risk of cataracts in subjects with type 2 diabetes [154]. Among the factors thought to induce lens opacification, oxidative damage is thought to be a major mechanism in the onset or progression of diabetic cataract (DC) [155]. Thus, researchers observed that the use of dietary antioxidant alleviates the cataract progression [156, 157]. Galactose is another substrate metabolized by AR and results in accumulation of galactitol, which also causes cataract formation. Studies on the anterior part of eyes showed that AR activation plays a key role in DC formation [158, 159]. AR inhibitors prevent cataract formation in streptozotocin (STZ)-diabetic animal models [77, 78] and galactose-fed rats [76]. Other than the effect of sorbitol, fructose metabolized from glucose in AR polyol pathway is another precursor that initiates production of AGE [79], which contributes to cataractous lenses of human subjects with diabetes [74]. Therefore, there is still an urgent need for ARI development. Since AR expression is low in wildtype mice, even in diabetes, Lee and colleagues generated the human AR expressing mice to accelerate cataractogenesis for the sugar cataract study [159]. We recently generated human AR transgenic (AR-Tg) mice that can shorten the time for DC formation by STZ injection [160], thus providing a useful laboratory model for studying DC formation and prevention. The role for AR in DC formation was further substantiated when it was observed that a lower level of diabetic cataract formed in AR null mice compared to wild type [161].

3.4.3 Diabetic retinopathy—Diabetic retinopathy (DR) is one of the major complications of diabetes and has become the leading cause of blindness in people of working age in the past century [75, 162]. Clinical features of DR are macular edema, retinal ischemia, retinal hemorrhages and microaneurysms, formation of intraretinal microvascular abnormalities, growth of neovascular vessels onto the retina, and retinal detachment [163]. Patients with DR experience a decline of visual acuity that affects many activities of daily living. Among the factors causing DR, vascular endothelial growth factor (VEGF) is considered a major one that leads to neovascularization in retina [164, 165]. Animal studies have also shown a correlation between elevated VEGF and diabetic vasculopathy [166]. Clinical trials have shown that use of the VEGF neutralizing antibodies by intravitreal injection improves visual acuity [167, 168]. Although anti-VEGF therapy has revolutionized management of DR, this procedure requires repeated injections, often monthly for two years, and may lead to impaired survival of neuronal and vascular cells [169]. Thus, alternative strategies are being sought to offset VEGF-driven pathology in the diabetic retina, such as reduction of VEGF protein production. In animal studies, genetic ablation of VEGF in Muller cells reveals the important role of VEGF production in retinopathy [170, 171]. Genetically predisposed diabetic mice (*db/db*) carrying a mutation in leptin receptor are type 2 diabetic models for investigation of DR [172–174]. Elevation of VEGF in the diabetic retina is decreased when the AR null mutation is introduced into *db/db* mice, which further prevents blood-retinal barrier (BRB) breakdown and apoptosis in retina [175]. Deletion of AR also prevents mice from streptozotocin-induced DR by inhibiting retinal capillary degeneration and superoxide generation [83]. Reduction of AR activity using inhibitors

helps to normalize VEGF levels [166], suppressing VEGF-induced tube formation in retinal endothelial cells [84] and alleviating hyperglycemia-induced damage in retinal pigment epithelial cells [80].

Considering the source of VEGF, Muller cells are believed to be the major immune cells that secrete VEGF in the diabetic eye [81]. However, our current unpublished studies show that genetic ablation of AR reduces hypoxia-induced VEGF secretion by attenuating COX-2 expression in retinal microglia (RMG) indicating that RMG could be another source of VEGF in retina (Fig. 5).

Other than anti-VEGF therapy, intravitreal injection of steroids is also used for treatment of diabetic macular edema [176]. Steroids are well-known to reduce inflammatory responses by suppressing NF-κB pathway [177, 178]. In the clinic, patients treated with intravitreal injections of steroids such as triamcinolone and dexamethasone showed improvement in diabetic macular edema by reducing central macular thickness [179]. However, these treatments have the side effects of causing cataracts. Nevertheless, suppression of NF-κB pathway is an effective strategy for prevention of onset and/or progression of DR which can be a blinding disease if left untreated.

Systemic inflammation is considered to be an intrinsic response to diabetes [180]. Inflammatory cytokines like interleukin-1β (IL-1β) and TNF-α are increased in the vitreous of patients with DR [181]. Increased TNF-α in retina leads to retinal vascular permeability [182], microglia activation [183] and induction of apoptotic protein markers [183] in retina. Collective data suggested that anti-inflammatory treatment with glucocorticoids [184] or minocycline [183] attenuates severity of retinopathy and helps to restore the BRB. Muller cells and RMG are thought to contribute to inflammatory responses in retina [163]. Our previous study showed that downregulation of AR reduces inflammatory responses in RMG [40] suggesting AR inhibition plays an alternative role in preventing DR by suppressing inflammatory responses in the diabetic eye.

Advanced glycation end-products (AGEs) have been shown to induce VEFG production [81] and matrix metalloproteinases (MMPs) [185] in the diabetic retina. Induction of MMPs alters the BRB by initiating morphological changes in retinal endothelial cells [185], which is often observed in DR. Amadori-glycated protein is the precursor to AGEs [46]. Patients with diabetes have increase of Amadori-glycated albumin (AGA) in serum [186] which correlates with higher risk of retinopathy [187]. Animal studies also showed the increase of AGA in the diabetic retina [188]. Inflammation in diabetic individuals could be induced by AGEs in kidney via NF-κB pathway [189] or by AGA in retina through Mitogen-activated protein kinases (MAPK) pathway [188]. Previous studies showed that AR inhibition or genetic deficiency suppresses the NF-κB [36–38] and MAPK pathways [39]. Therefore, it would be an interesting question whether AR mediates AGE or AGA-induced inflammatory responses in diabetic retina. Recent studies have shown that RMG were activated in the presence of AGE [190, 191] and AGA [188], and follow the induction of TNF-α. Our current unpublished data observed that AR inhibition suppresses AGA-induced TNF-α secretion and cell migration in RMG suggesting that AR is involved in AGA-mediated DR (Fig. 4).

3.4.4 Posterior capsule opacification—Posterior capsule opacification (PCO), which is the complication after cataract surgery [192], results from abnormal proliferation and migration of lens epithelia cells (LECs) [193] in the central posterior capsule resulting in degraded visual acuity. LECs undergo differentiation from an epithelial to a myofibroblast phenotype [100] and matrix contraction [194], which further leads to opacification. TGF-β overexpression in Tg mice led to morphological changes in lens that resembled PCO in human [195]. In the process of PCO, TGF-β plays an important role in developing epithelial-mesenchymal-transition (EMT) [100], resulting in expression of EMT related markers such as α-smooth muscle actin (α-SMA) [194], and forming cells with a spindled-shaped myofibroblastic morphology [100]. TGF-β also induces MMPs such as MMP-2 and -9, which has been demonstrated that can be induced under mechanical trauma of cataract surgery [194]. Therefore, suppression of EMT and MMPs activation could lead to prevention of PCO. Previous works showed that AR inhibition suppresses LPS or high glucose-induced MMP-9 activation [40, 196, 197]. Kidney studies further reported that TGF-β-induced MMPs and EMT activations were attenuated by AR inhibitor treatment in renal cells [101, 198]. Yadav and colleagues reported a study using pig capsule that AR inhibitor were shown to reduce LECs proliferation and expression EMT markers [199]. SMAD signaling pathway has been identified as playing a critical downstream role in TGF-β-mediated signaling [200]. TGF-β interaction with its receptor leads to SMADS phosphorylation and subsequent translocation to the nucleus to trigger EMT process [201]. Recently, an encouraging study in LECs showed that AR inhibition suppresses TGF-β2-induced SMADs phosphorylation and its downstream regulatory pathways including cell migration, EMT initiation and MMPs activation [202]. A novel function of AR was reported, involving AR interaction with SMADs. This novel model offers a possible mechanism to explain how AR inhibitor treatment suppresses SMADs activation [202]. This finding indicated the AR is required to facilitate TGF-β/SMADs pathway and AR inhibitor disrupts AR-SMADs interaction. Accordingly, AR could be a therapeutic target for PCO.

4 Summary and future directions

4.1 N ovel AR inhibito rs

In the view of AR inhibitor and ocular inflammation, we determined whether β-glucogallin (BGG), isolated from Indian gooseberry, is an efficacious AR inhibitor. We observed that BGG is a potential anti-inflammatory agent against endotoxin-induced uveitis in an experimental mouse model. BGG not only alleviated inflammatory responses in macrophages but also suppressed infiltration of immune cells into the eye [39]. However, our extensive research showed the instability of BGG in thermal acidic condition [203]. We observed that the ester linkage in BGG (glycosyl 1-ester) is labile in aqueous solution. Thus, our collaborators Dr. Daniel LaBarbera and his lab designed β-glucogallin amide (BGA), a derivative of BGG produced by replacing the ester with an amide linkage to join the gallic acid and glucose ring. BGA demonstrated similar inhibitory activity *in vitro* and *ex vivo* but much better stability under thermal acidic condition [203]. With compatible activity and greatly improved stability, BGA holds a promise to be an attractive therapeutic lead toward the treatment of ocular inflammation. Further structure-based drug design is

presently ongoing to improve the pharmacological profile of BGA, and more sophisticated animal models will be used to test BGA efficacy in vivo.

Our studies of BGG were motivated by strong animal study results which showed that this AR inhibitor can prevent complications of diabetes mellitus. Clinical trials of many AR inhibitors have been unsuccessful in part due to toxicity from their metabolic breakdown products. In our studies of the effect of AR inhibition on inflammation associated with endotoxin-induced uveitis, we included Sorbinil as a positive AR inhibitor control. Sorbinil is no longer considered a candidate for human therapy because previous clinical studies showed that microsomal metabolites of Sorbinil are cytotoxic [204]. Similarly, other AR inhibitors such as Imirestat [205], Tolrestat [206, 207] and Zoporestat [207] also failed in clinical trials due to liver and/or renal toxicity. So far, only Epalrestat has been shown to be safe and efficacious against diabetic peripheral neuropathy and is now marketed in Japan [121, 207]. Therefore, the encouraging results of BGG and preliminary data from BGA provide a new direction for development of AR inhibitors based on a novel pharmacophore structurally unrelated to previously failed AR inhibitors. Since BGG is abundant in many fruits consumed by humans (gooseberry, rhubarb), it is likely that it will not cause liver and renal complications.

In the study of DR, we wanted to know whether BGG is capable of preventing diabetic complications. We developed hyperglycemic condition using high glucose medium on ARPE-19 cells. We found that BGG is an efficacious AR inhibitor reducing hyperglycemia-induced cell death, ROS production, ER stress and mitochondrial dysfunction [80]. Hyperglycemia also elevates the level of advanced glycation end products (AGEs) in the serum of diabetic patients [186]. A study on AGEs has been known to induce ocular inflammation by triggering RMG activation [148]. Our preliminary studies showed that AR inhibition attenuates amadori glycated albumin (AGA)-induced inflammatory responses in RMG (Fig. 4). The mechanism behind this finding remains unknown and should be studied. Since low cytotoxicity of BGG has been shown in cell line model [39], extensive studies of BGG in animal study are feasible. Diabetes shows higher risk in elevating VEGF in retina that causes neovascularization [164, 165]. Our preliminary showed that pharmacological inhibition or genetic ablation of AR prevents hypoxia-induced VEGF secretion from RMG (Fig. 5). Based on our previous study of ARI on RMG, We believe that BGG and BGA are a potential therapeutics for diabetic complication by preventing RMG activation in diabetic retina. However, to further apply BGA to next step, more pharmaceutical kinetics and toxicity experiments are necessary. Although BGA is derived from natural compound, the toxicity *in vivo* has not been studied. Animal toxicity study of BGA injection should be conducted before BGA's further application. Since BGA was designed for its higher stability, *in vivo* pharmaceutical kinetics should also be studied in the future.

4.2 A role for AR in ocular inflammation

In the eye, RMG is one of the immune cells that normally reside in the inner retina. However, under inflammatory conditions, RMG can be found in higher numbers in the subretinal space between photoreceptor outer segments and the RPE. Activated RMG secrete chemokines and/or cytokines to damage neural and retinal cells in the eye.

Therefore, regulation of RMG may be critical for preventing ocular inflammation. To investigate a more specific area of the eye, we conducted an *ex vivo* study to examine a potential role for AR in the response of RMG to endotoxin exposure. We observed that inflammatory responses in RMG following exposure to endotoxin were substantially suppressed when cells were treated with AR inhibitors or were genetically deficient for AR gene expression. These results demonstrated that pharmacological inhibition or genetic ablation of AR prevents endotoxin-induced inflammation in the retina by suppressing RMG activation [40]. An MMP-9 inhibitor, designed to inhibit gelatinase activity, was shown to prevent LPS-induced cell migration. By a different route, AR inhibition prevents cell migration by reducing MMP-9 protein expression. Therefore, one would expect additive effects of combined treatment with AR and MMP inhibitors on preventing cell migration. A preliminary animal study was extensively performed using CX3CR1 transgenic mice, a strain in which monocytes, including RMG, constitutively express green fluorescence protein and therefore are easily observed in ocular tissue sections. We observed that LPS injection triggers RMG activation and migration into inner and outer nuclear layers (Fig. 6). Co-injection with Sorbinil alleviated LPS-induced RMG activation and migration in the retina (Fig. 6) indicating that AR inhibition is valid *in vivo* to prevent ocular inflammation. In inflammation, TNF-α plays a robust role in causing apoptosis. We have previously shown that downregulation of AR by either pharmacological inhibition or genetic ablation reduces TNF-α secretion in RMG as well as apoptosis in co-cultured RPE cells [40]. Studies on the detection the level of TNF-α secretion and apoptosis in retina should be conducted in the future. Since we have AR null mice, genetic effects of AR on LPS-induced RMG activation would be a convincing experiment to confirm the role of AR in retinal inflammation. The study of RMG provides a therapeutic target in the retina for AR-associated ocular inflammatory diseases such as uveitis and retinopathy. In addition, Muller cells are the glial cells that have immune functions in the eye. AR was also reported to express in the Muller cells [208, 209]. Several studies showed that Muller cells are involved in uveitis, proliferative vitreoretinopathy (PVR) and DR [210–212]. Therefore, the effect of AR on Muller cells is an interesting study to be conducted in the future.

In the experimental uveitis model or hyperglycemic stress experiment, we treated the mice or cell line at the same time while uveitis or hyperglycemic stresses were being induced. However, in real practice, treatment is always applied after disease occurs. Based on this point, the efficacy of AR inhibitors after stressor such as LPS or hyperglycemia needs to be tested. Although we haven’t conducted experiments regarding this issue, administration of AR inhibitors after retinal inflammation or hyperglycemia would better mimic the treatment paradigm in uveitis or diabetes management. It is possible that the effect of post-treatment would be less effective than pre-treatment due to some possible irreversible changes that may have occurred or the disease may have gone to a more advanced stage that is less susceptible to ARI therapy.

We observed that AR inhibitors lowered the abundance of inflammatory cells in the vitreous of endotoxin-treated animals. One possibility is that inhibitors reduce expression of MMPs and thereby reduce the ability of cells to migrate toward their targets. Another possible explanation for reduced immune cell infiltration may relate to their ability to pass through the vascular endothelium. Adhesion molecules are cell surface receptors that

facilitate the binding of immune cells to endothelial cells and penetration [213]. These adhesion molecules include intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM). TNF-α is an inflammatory cytokine that mediates pathological endothelial changes which cause induction of adhesion molecule expression and vascular leakage at the site of inflammation [214]. Ramana and colleagues reported that AR inhibition prevents TNF-α-induced increases of ICAM-1 and VCAM in human umbilical vein endothelial cells (HUVECs) as well as decreases monocytes adhesion to these cells [215]. This observation may provide another explanation for the effect of AR inhibitors on prevention of inflammatory cells infiltration into the eye.

4.3 Studies of AR as a mediator of EMT during development of posterior capsule opacification

Regarding the effect of AR inhibitor on PCO development, we proposed a novel idea of AR with a noncatalytic function. We observed AR interacts with Smads in a NADPH-dependent pathway but in a manner not requiring enzymatic activity [202]. This is the first paper that reports a non-enzymatic function of AR. We also found that AR inhibition or genetic ablation prevents TGF-β2-induced Smads activation and expression of EMT markers, thus indicating a potential therapeutic strategy for prevention of PCO development. However, remaining unknown are the details of how AR interacts with Smads and whether there is a distinct interaction site. Sequence deletion could be used for understanding the possible site or domain. Since AR null mice are available, we can develop PCO in either wildtype or AR null mice to confirm the hypothesis *in vivo*. Sorbinil disruption of AR-Smads interaction could be resulted from an AR conformational change or actual blocking of a protein-protein interaction site. In this study, we only tested the noncatalytic function of AR using Sorbinil. However, whether other ARIs such as BGG also contribute similar effect is still unknown. Other ARIs may fail to disrupt AR-Smads interaction due to different results of conformational change or blocking site. Therefore, more studies on different ARIs on noncatalytic effect need to be conducted to elucidate the hypothesis.

Most of the published studies surrounding Sorbinil as an anti-inflammatory agent implicitly presume its efficacy derives from inhibition of AR catalytic activity. In our PCO study, we showed that a catalytically inactive mutant of AR was able to facilitate TGF-β2-induced Smad activation, demonstrating that the ability of Sorbinil to downregulate Smad activation was unrelated to its ability to inhibit AR catalysis. Therefore, the effect of Sorbinil can be segregated into its effects on catalytic and noncatalytic functions of AR. Previous studies reported that AR plays a catalytic role in reduction of aldehydes during lipid peroxidation pathway following NF-κB activation [20, 21] and AR inhibitors such as Sorbinil suppress this pathway [23, 25–27]. However, the noncatalytic role of AR in NF-κB activation has not been studied to date. Going forward, it would be possible to address this question by transfecting AR null cells with wildtype AR (wtAR) or an active site mutant AR (mutAR) and treat the cells with or without AR inhibitors (Sorbinil or BGG) under LPS exposure. If LPS induces the same level of NF-κB activation in mutAR group compared to wtAR group, one could conclude that AR facilitates NF-κB activation in a noncatalytic fashion. Similarly, if Sorbinil treatment prevented NF-κB activation in both groups, it would be consistent with

the notion that an AR interaction domain overlapping the ARI binding site is important for NF-κB activation in a manner similar to our findings with AR and Smad activation.

AR has been studied extensively as a catalyst that results in sorbitol accumulation and contributes to pathogenesis of diabetic complications. Our current pharmacological studies confirm the importance of AR through its role as a regulator of glucose metabolism through the polyol pathway (catalytic function). In addition, we have compelling results which point to AR as a component of the TGF-β signaling pathway (noncatalytic function). It will be exciting to see the results of future studies which aim to further clarify the mechanism linking AR to TGF-β signaling and possible therapeutic strategies to prevent TGF-β-associated disease.

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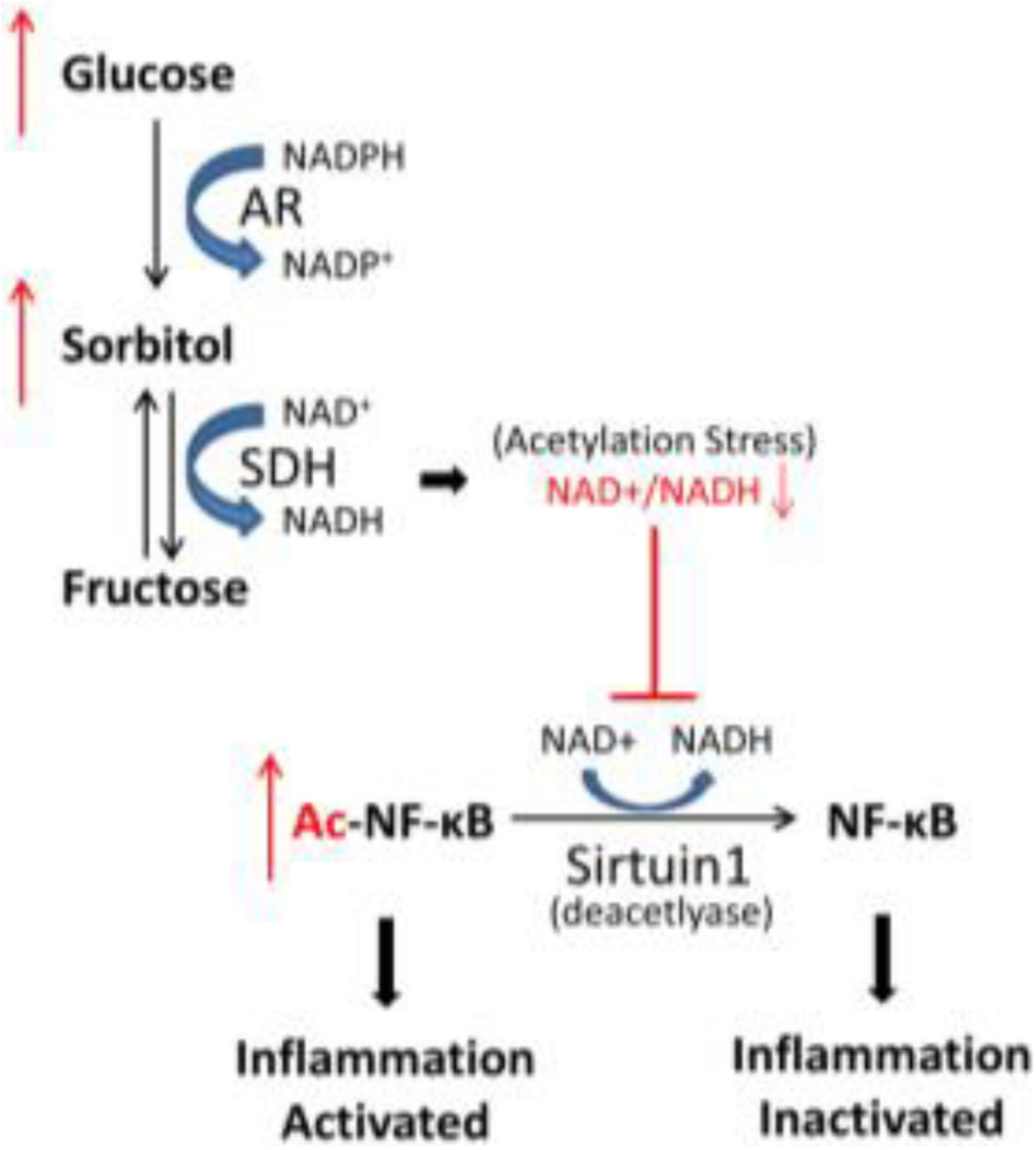

Fig. 1.

Linkage between polyol pathway activation and induction of inflammatory signaling. Glucose metabolism through the polyol pathway results in a reduced NAD^+/NADH ratio, which lowers the ability of Sirt1 to deacetylate NF-κB.

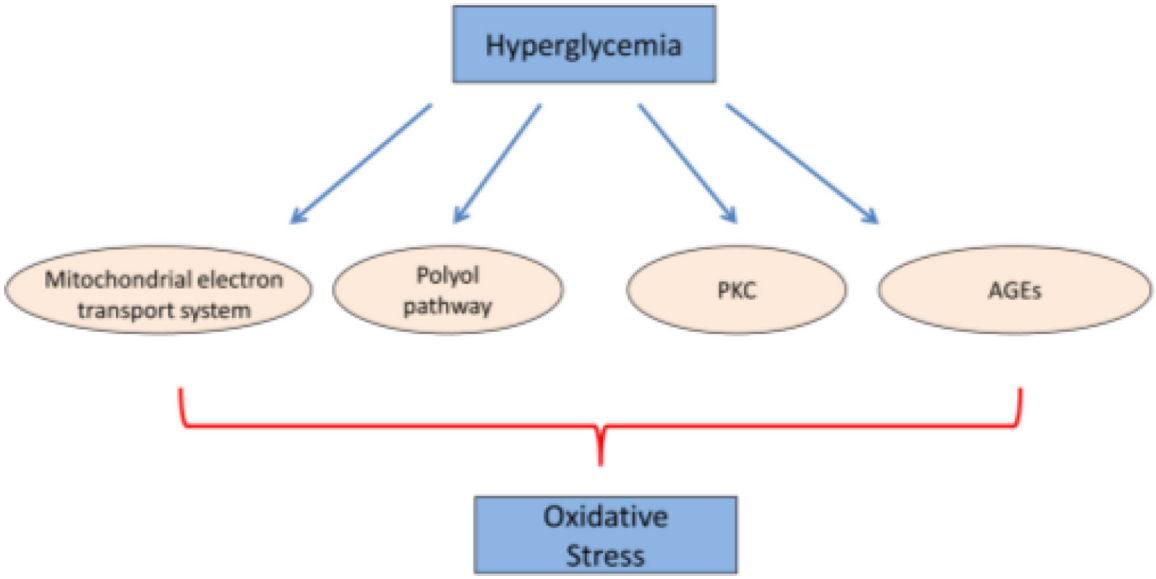

Fig. 2.

Hyperglycemia-induced oxidative stress is contributed by mitochondrial electron transport system, polyol pathway, PKC and AGEs.

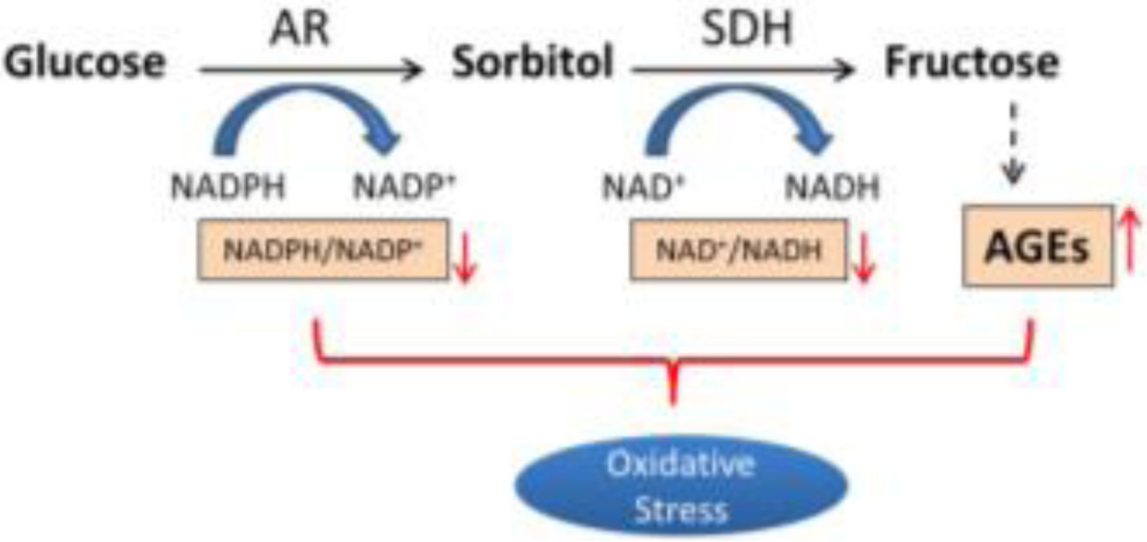

Fig. 3.

Increased flux of polyol pathway initiates oxidative stress by reducing the ratio of NADPH/$NADP^+$ and NAD^+/NADH, and inducing AGEs production.

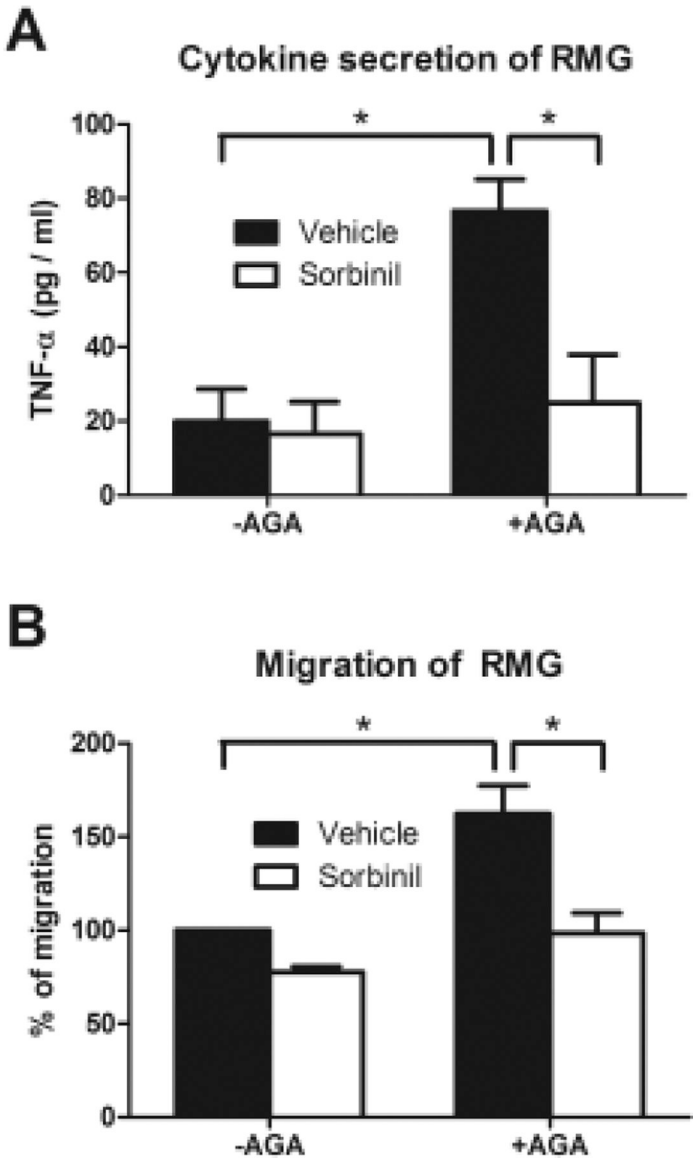

Fig. 4.

Effect of ARI on AGA-induced cytokine secretion and migration in RMG. RMG were treated with vehicle or Sorbinil (10 μM) in the absence or presence of AGA (500 μg/ml) for 24 h for TNF-α secretion (A) or migration assay (B). Secreted TNF- α was measured by using mouse TNF-α detection ELISA kit. The migration assay was conducted by using transwell method. Data shown are means ± SEM (N = 3). **P* < 0.05.

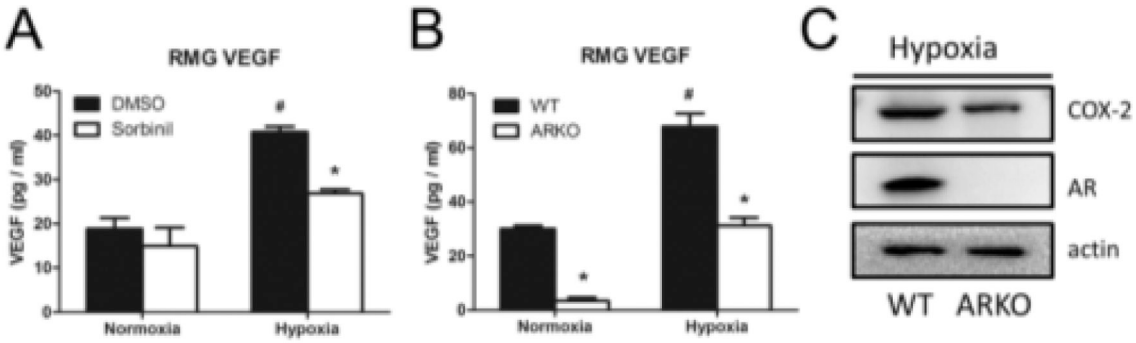

Fig. 5.

AR inhibition or knockdown prevents hypoxia-induced VEFG secretion by reducing COX-2 expression. RMG were treated with 10 μM Sorbinil (A) or isolated from ARKO mice (B) in normoxia or hypoxia (1% O_2) condition for 24 h. Secreted VEGF was measured by using mouse VEGF detection ELISA kit. Hypoxia-induced COX-2 expression in wild type (WT) or ARKO RMG was probed by using Western blot (C). Data shown are means ± SEM (N = 3). $*P$, $^{\#}P < 0.05$.

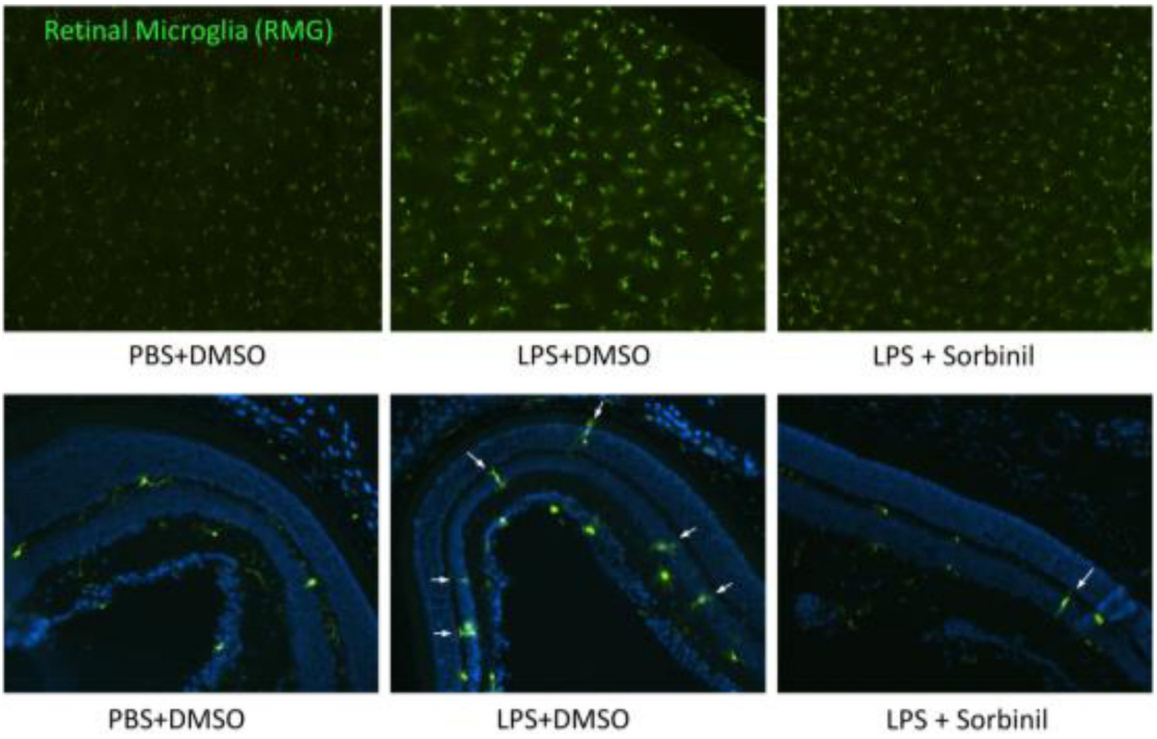

Fig. 6.

AR inhibition prevents RMG activation and migration under LPS exposure. Cx3Cr1 transgenic mice were injected with LPS (500 ug / mouse) for 24 h with or without Sorbinil co-injection. Green spots indicate RMG in retinas. White arrows indicate RMG migration into inner or outer nuclear layers. Figure adapted by Chang and Petrash from *Biochem Biophys Res Commun*. 2016; 473(2):565–571.

Table 1.

The table for human aldo-keto reductase family 1B

Gene	Protein	Also known as	Chromosomal localization
AKR1B1	Aldose reductase	AR, ALR2	7q35
AKR1B10	Small intestine-like aldose reductase	HSIR, ALR1	7q33
AKR1B15	Aldo-keto reductase family 1, member B15	AKR1B10L	7q33

Table 2.

The table for the role of AKR1B1 in health and disease.

Organ	Associated disease
Heart	*Myocardial ischemic injury*
	Cardiomyopathy
Kidney	*Diabeitc Nephropathy*
	Acute Kidney Injury
Nerve	*Diabetic peripheral neuropathy*
	Cardiac autonomic neuropathy
Eye	*Uveitis*
	Diabetic cataract
	Diabetic retinopathy
	Posterior Capsular Opacification