Novel drugs and their targets in the potential treatment of diabetic retinopathy

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Source of support: Deanship of Scientific Research (RGP-VPP-052) at King Saud University

Diabetic retinopathy (DR) is the most common complication of diabetes. It causes vision loss, and the incidence is increasing with the growth of the diabetes epidemic worldwide. Over the past few decades a number of clinical trials have confirmed that careful control of glycemia and blood pressure can reduce the risk of developing DR and control its progression. In recent years, many treatment options have been developed for clinical management of the complications of DR (e.g., proliferative DR and macular edema) using laser-based therapies, intravitreal corticosteroids and anti-vascular endothelial growth factors, and vitrectomy to remove scarring and hemorrhage, but all these have limited benefits. In this review, we highlight and discuss potential molecular targets and new approaches that have shown great promise for the treatment of DR. New drugs and strategies are based on targeting a number of hyperglycemia-induced metabolic stress pathways, oxidative stress and inflammatory pathways, the renin-angiotensin system, and neurodegeneration, in addition to the use of stem cells and ribonucleic acid interference (RNAi) technologies. At present, clinical trials of some of these newer drugs in humans are yet to begin or are in early stages. Together, the new therapeutic drugs and approaches discussed may control the incidence and progression of DR with greater efficacy and safety.

Key words: diabetic retinopathy • drugs • neurodegeneration • retina • oxidative stress • hyperglycemia

Full-text PDF: http://www.medscimonit.com/download/index/idArt/883895
Background

Diabetic retinopathy (DR) is one of the major complications of diabetes, leading to vision loss and blindness. According to a recent report by the World Health Organization (WHO), approximately 346 million people worldwide have diabetes, approximately 10% of diabetic people have severe visual impairment, and 2% become blind [1]. In the last few decades a number of hyperglycemia-induced metabolic stresses (e.g., the activation of protein kinase C [PKC], poly[ADP-ribose] polymerase [PARP], and increased flux through the hexosamine pathway, and the accumulation of polyols and advanced glycation end-products [AGEs]) have been implicated in the pathophysiology of diabetes via the increased production of reactive oxygen species (ROS) [2]. The recognition of these processes and pathways has led to the investigation and development of potential targets and corresponding therapeutic agents for the prevention and treatment of DR. Other processes associated with DR include the acceleration of inflammatory responses, the upregulation of the renin-angiotensin system (RAS), and the dysregulation of growth factors, which have been discussed in a number of recent review articles [3,4].

Despite the continuous efforts of researchers toward a better understanding of the pathophysiology of the disease, the identification of potential targets for the treatments of diabetic retinopathy remains a challenge. Future therapies would likely involve the inhibition of several different pathways or the discovery of a master regulator molecule(s) and their inhibitors to be used for DR treatment. In this review, we discuss recent advances in discovering potential drug targets and their corresponding therapies that have shown great promise in the treatment of DR (Tables 1 and 2). However, clinical trials for some of these drugs are yet to begin or are in the early stages, but it is hoped that these potential drugs would be safe and effective in treatment of the DR. We anticipate that this discussion will provide a better understanding of the new treatment strategies for the control of DR.

Inhibition of Hyperglycemia-Induced Metabolic Stresses

Advanced glycation end-product (AGE) inhibitors

Numerous studies have demonstrated the pathological role of AGEs in the initiation and progression of diabetic retinopathy [5]. In diabetes, the accumulation of AGEs and their interactions with their receptors (RAGEs) are increased, adversely affecting the retinal microvasculature in patients with diabetes [6,7].

AGE inhibitors have been used in experimental studies to modulate the action of AGEs in the pathogenesis of diabetic retinopathy. Aminoguanidine, a specific inhibitor of AGE formation, prevents AGE accumulation at the branching sites of precapillary arterioles, leading to diminished pericyte drop-out, reduced progression of vascular occlusion, and inhibited abnormal endothelial cell proliferation in diabetic dogs [8]. In addition, pyridoxamine treatment, another inhibitor of AGE formation, protects against capillary drop-out, limits the upregulation of laminin protein, and limits the increase in AGEs in the retinal vasculature of diabetic rats [9]. A number of other AGE inhibitors (e.g., OPB-9195, ALT-946, ALT-711, the RAGE inhibitor LR-90, and the putative cross-link breakers N-phenacylthiazolium bromide [PTB] and alagebrium) have been developed [6,10,11]. The systematic administration of the soluble form of RAGE (sRAGE) inhibited blood-retinal barrier breakdown, leukostasis, and the expression of ICAM-1 in the retinas of diabetic mice [12]. Thus, the inhibition of AGE formation, blockade of the AGE-RAGE interaction, and suppression of RAGE expression may be useful therapeutic targets for treating the complications of diabetic retinopathy.

The process of AGE-induced retinal leukostasis and hyperpermeability has been shown to be inhibited by pigment epithelium-derived factor (PEDF), which blocks superoxide generation and NF-kB activation in AGE-exposed endothelial cells [13]. PEDF is also a potential anti-oxidative agent and anti-inflammatory factor that may block the AGE-RAGE interaction, thereby ameliorating the progression of proliferative diabetic retinopathy (PDR) [14,15].

Protein kinase C (PKC) inhibitors

The increased activities of the classic protein kinase C (PKCs) isoforms (PKC-α, βI/2, and PKC-δ) in diabetes greatly enhance the de novo synthesis of diacylglycerol (DAG), which has been linked to vascular dysfunction and the pathogenesis of DR [16].

Some selective PKC isoform inhibitors are likely to be able to delay the progression of diabetes-associated visual and vascular pathogenesis. One of the first PKC inhibitors, PKC412, reduced the effects of several isoforms of PKC and improved visual acuity when administered orally (100 mg/d) to patients with diabetic macular edema (DME) [17]. In the diabetic retina, the isoform PKC-β is highly expressed; thus, the selective inhibition of PKC-β by ruboxistaurin mesylate has been widely studied [18]. Eli Lilly Co., USA, has designed a specific inhibitor of the PKC-β isoform, ruboxistaurin, which has shown beneficial effects in animal models of DR [19]. The effect of ruboxistaurin in a clinical trial for Protein Kinase C beta-Inhibitor Diabetic Retinopathy Study (PKC-DRS) in patients with moderately severe to very severe non-proliferative diabetic retinopathy suggested that the drug was well tolerated and delayed the time to occurrence of moderate visual loss, but did not prevent DR progression [20]. Another clinical trial for Protein Kinase C beta Inhibitor Diabetic Retinopathy Study (PKC-DRS2) demonstrated that the drug-treated patients experienced significantly less sustained moderate visual loss [21,22]. More recently, the combined data from 2
### Table 1. An overview of the potential drugs and their targets early in the treatment of diabetic retinopathy.

| Targets                               | Drugs                                      | Potency | References |
|---------------------------------------|--------------------------------------------|---------|------------|
| Inhibitor of AGE formation            | Aminoguanidine                             | High    | [8]        |
|                                       | Pyridoxamine                               | High    | [9]        |
|                                       | OP8-9195, ALT-946, ALT-711, RAGE inhibitor, LR-90, Putative cross-link breaker N-PheracylThiazolium Bromide (PTB) and alagebrium | Fair    | [6,10,11] |
| Protein Kinase C (PKCs) inhibitors    | PKC412                                     | Good    | [17]       |
|                                       | Ruboxistaurinmesylate                      | High    | [18]       |
|                                       | Ruboxistaurin (RBX)                        | High    | [19–23]    |
| Aldose Reductase Inhibitors (ARIs)    | Sorbinil                                   | High    | [30]       |
|                                       | Tolrestat, Lidoestat, Zenarestat, Ponalrestat and Zopolestat | Fair    | [28,31]    |
|                                       | ARI-809                                    | High    | [28]       |
|                                       | Epalrestat, Fidarestat and Ranirestat      | Good    | [29,31,32] |
| Nonsteroidal Anti-Inflammatory Drugs (NSAID) | Aspirin                                   | Good    | [35,38]    |
|                                       | Nepafenac, Sodium salicylate and Sulfasalazine | Good    | [40,41]    |
|                                       | Baicalein and Genistein                    | Fair    | [44,45]    |
|                                       | Nepafenac, Celecoxib                       | Good    | [40,43]    |
| Lipid lowering drugs                  | Fenoestrilate, statins, simvastatin        | Fair    | [76,77]    |
| Neuroprotective, N-methyl D-aspartate (NMDA) receptor antagonist | MK-801, Memantine                         | Good    | [77,78]    |
| Stem cells as a therapeutic option    | Hematopoetic stem cells, bone marrow-derived mononuclear cells | Good    | [92–94]    |
| Ribonucleic acid (RNA) interference   | HIF-1α siRNA, VEGF siRNA, Bevasiranib, siRNA-027 and RTP801i | Good    | [97,99–102] |

### Table 2. An overview of the potential drugs and their targets early in the treatment of DR.

| Targets                               | Drugs                                      | Potency | References |
|---------------------------------------|--------------------------------------------|---------|------------|
| Poly (ADP ribosylated) protein (PARP) inhibitors | PJ-34, 3-aminobenzamide and 1,5 isoquinolinediol | Good    | [43,44,46,47] |
|                                       | 1,5-iso-quinolinediol (ISO) and 10-(4-methyl-piperazin-1-ylmethyl)-2H-7-oxa-1,2-diaza-benzo-[de] anthracen-3-1 (GPI-15427) | Fair    | [48]       |
| NF-κB inhibitors                      | Dehydroxymethyloxquinomycin (DHMEQ), Pyrrolinedithiocarbamate | Good    | [50,54]    |
| Angiotensin 2 receptor blockers /angiotensin converting enzyme (ACE) inhibitors | Valsartan, PD123319                          | Fair    | [57]       |
|                                       | Candesartan, losartan and candesartan cilexetil | Fair    | [58–60]    |
|                                       | Lisinopril, Perindopril                    | Fair    | [63,64]    |
| Antioxidants                          | Alpha-lipoic, taurine, alpha-tocopherol, N-acetyl cysteine, ascorbic acid, beta carotene, Vitamin C and Vitamin E, Benfotiamine | Fair    | [68–70]    |
| Lipid lowering drugs                  | Fenoestrilate, statins, simvastatin        | Fair    | [76,77]    |
| Neuroprotective, N-methyl D-aspartate (NMDA) receptor antagonist | MK-801, Memantine                         | Good    | [77,78]    |
| Stem cells as a therapeutic option    | Hematopoetic stem cells, bone marrow-derived mononuclear cells | Good    | [92–94]    |
| Ribonucleic acid (RNA) interference   | HIF-1α siRNA, VEGF siRNA, Bevasiranib, siRNA-027 and RTP801i | Good    | [97,99–102] |
clinical studies (PKC-DRS and PKC-DRS2) for ruboxistaurin treat-
ments in diabetic retinopathy patients suggest beneficial effects on vision loss, vision gain, and reduced need for initial focal laser therapy, especially in case of diabetic macular edema [23].

Thus, inhibitors of PKCs, especially PKC-β, are likely to be potential candidates for the early treatment and management of some of the pathologies of DR.

Aldose reductase inhibitors (ARIs)

In diabetes, the polyol pathway of glucose metabolism becomes activated to produce sorbitol by the enzyme aldose reductase (AR) [24]. As a result, cells are deprived of glutathione, an endogenous antioxidant, which thus increases oxidative stress [25,26].

Numerous studies have shown that aldose reductase inhibitors (ARIs) decrease the prevalence of microneurysms, basement membrane thickness, oxidative stress, VEGF expression, neuronal apoptosis, and glisost in the retina in diabetic ani-
mals [27–29]. Sorbinil, the first ARI to undergo clinical trials, showed little effect in controlling or preventing the development or progression of DR [30]. Several ARIs that have been developed over the last 2 decades (e.g., tolorestat, lidorestat, and zenarestat) have been found to have hepatic and renal toxicity. Ponalrestat and zopolrestat, which have better safety profiles, also showed better potency. However, clinical studies demonstrated only a minor benefit, possibly due to insufficient inhibi-
tion of the pathway [28,31]. A new ARI, ARI-809, has a high selectivity for aldose reductase and has greater potency [28]. Other representatives of new structural classes of ARIs (e.g., epalrestat, fidarestat, and ranirestat) have been studied in diabetic animals with great success, and it is hoped that these drugs will prove useful in the treatment of diabetic retinopathy [29,31]. The oral administration of fidarestat in a strep-
tozotocin-induced diabetic rat model has been shown to inhibit the loss of retinal capillaries in diabetic rats in conjunction with an inhibition of the diabetes-induced activa-
tion of NF-κB, which mediates inflammatory responses [41]. In another study, the pericorneal injection of celecoxib-poly-lactide-co-glycolide micro-particles was found to reduce VEGF mRNA and vascular leakage in diabetic animals [40,42,43]. Two other anti-inflammatory drugs – baicalein and genistein – suppressed diabetes-induced inflammatory processes and inhibited vascular abnormalities and neuron loss in diabetic retinas [44,45].

The topical application of the COX-2 inhibitor nepafenac (via eye drops) inhibited diabetes-induced increases in vascular lesions and PGE2, superoxide, and COX-2 production [40,43]. The oral administration of celecoxib, a potent COX-2 inhibitor, reduced VEGF mRNA and vascular leakage in animals. A phase III study evaluating celecoxib in patients with diabetic retinopathy is currently ongoing.

Anti-Inflammatory Drugs for the Treatment of DR

Numerous functional and molecular mediators of inflammation, including the recruitment and activation of leukocytes, have been detected in the retinas of diabetic animals. Proinflammatory cy-
tokines and chemokines and other inflammatory markers con-
tribute to capillary nonperfusion in DR [35]. Under the pathological conditions of DR, the inflammatory response upregulates inducible nitric oxide synthase (iNOS), nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), intracellular adhesion mole-
cule (ICAM-1), vascular endothelial growth factor (VEGF), pros-
taglandin E2, interleukin 1β (IL-1β), and cytokines, increasing permeability and leukostasis in retinal capillaries [36,37]. The discovery of inflammatory events associated with microvascular damage in DR has led the interest in the early treatment of DR.

In animal models of diabetes, the use of daily doses of non-
steroidal anti-inflammatory drugs (NSAIDs) can protect against diabetic retinal microangiopathy and damage to the vascular-
ture [35]. Aspirin, at doses ≤0.6 mmol/l, prevented the apoptosis of capillary cells and the development of acellular cap-
illaries in a streptozotocin-induced diabetic rat model [38]. A high dose of aspirin inhibited blood retinal barrier breakdown in diabetic rats; this inhibition was accompanied by the inhibi-
tion of the retinal expression of ICAM-1, a reduction in the ad-
hesion of leukocytes to the retinal vasculature, and lower ret-
inal expression of eNOS and NF-κB [39]. Aspirin has also been shown to inhibit inflammatory mediators, iNOS, and the produc-
tion of nitric oxide. The administration of topical nepafe-
nac, which has unique time-dependent inhibitory properties against COX-1 and COX-2, has been shown to inhibit diabetes-
duced microvascular abnormalities with no adverse effects on neuronal degeneration [40]. Salicylate drugs (aspirin, sodium salicylate, and sulfasalazine), etanercept (a soluble recep-
tor of TNFα), and meloxicam (an inhibitor of COX-2) have been found to inhibit the loss of retinal capillaries in diabetic rats in conjunction with an inhibition of the diabetes-induced activa-
tion of NF-κB, which mediates inflammatory responses [41].

The topical application of the COX-2 inhibitor nepafenac (via eye drops) inhibited diabetes-induced increases in vascular lesions and PGE2, superoxide, and COX-2 production [40,43]. The oral administration of celecoxib, a potent COX-2 inhibitor, reduced VEGF mRNA and vascular leakage in animals. A phase III study evaluating celecoxib in patients with diabetic retinopathy is currently ongoing.

Poly (ADP ribose) Protein (PARP) Inhibitors

PARP is a nuclear enzyme that is generally present in the in-
active form in cells but is activated in the retinas of diabetic ani-
mals, causing DNA damage and increasing oxidative and nitrosative stress [43]. PARP inhibits the activity of glycer-
dehyde 3-phosphate dehydrogenase (GAPDH), inducing the
activation of the hexosamine pathway, protein kinase C (PKC), and AGE formation, which triggers the production of reactive oxygen and nitrogen species.

The specific PARP inhibitor PI-34 inhibits the diabetes-induced increase in TUNEL-positive (apoptotic) cells and inhibits early vascular lesions of DR [46]. PI-34 also inhibits diabetes-induced leukostasis in the retina [47]. Other structurally unrelated PARP inhibitors (3-aminobenzamide and 1,5isoquinolinediol) inhibit the diabetes-induced increase in VEGF expression. In diabetic rats, PARP inhibitors have been shown to inhibit the activation of NF-κB and the induction of the expression of inflammatory proteins [43]. Diabetic mice treated with PI-34 for 6 months exhibited inhibition in both the loss of pericytes and the formation of acellular capillaries [44]. Recently, Drel et al showed that the PARP inhibitors 1,5-iso-quinolinediol (ISO) and 10-(4-methyl-piperazin-1-ylmethyl)-2H-7-oxa-1,2-diazabenzode [a]anthracen-3-1 (GPI-15427) reduce diabetes-induced retinal oxidative-nitrosative and endoplasmic reticulum stress and glial activation [48]. The increase in the number of TUNEL-positive nuclei in the retinas of diabetic rats was prevented by ISO and GPI-15427. Thus, the inhibition of PARP is a promising therapeutic target to inhibit the development of diabetic retinopathy.

**NF-κB Inhibitors**

NF-κB is a transcriptional factor that is activated in the diabetic retina. NF-κB subunits accumulate in the endothelial and glial cells of the epiretinal (e.g., MCP-1 and sICAM), which are involved in the pathogenesis of PDR [49,50].

The use of dehydroxymethylpoxyquinomicin (DHMEQ), an NF-κB inhibitor, attenuates the retinal expression of angiotensin II and AT1-R and other inflammatory parameters in the diabetic retina [50]. Several different antioxidants inhibit the diabetes-induced activation of retinal NF-κB [47,51]. The inhibitor DHMEQ has been shown to suppress cytokine expression in vitro [52] and to inhibit tumor growth and angiogenesis in vivo [53]. In another study, the inhibition of NF-κB led to the suppression of VEGF and ICAM-1 in the diabetic retina [50]. NF-κB inhibition with pyrrolidinedithiocarbamate led to the suppression of ischemia-induced retinal neovascularization [54]. Thus, NF-κB inhibitors may be potential agents for ameliorating the complications of diabetic retinopathy.

**Angiotensin 2 Receptor Blockers/Angiotensin-Converting Enzyme Inhibitors**

Hypertension has been identified as a major risk factor of microvascular complications, which are characteristic of DR. Several studies on the components of the retinal renin angiotensin system (RAS), rennin, angiotensin-converting enzyme (ACE), and angiotensin types I and II, have shown increased levels of prorenin, renin, and Ang-2 in the vitreous humor of patients with PDR and diabetic macular edema (DME), suggesting the involvement of the RAS in the pathogenesis of DR [55,56].

The RAS activates downstream inflammatory responses by upregulating VEGF, ICAM-1, MCP-1, and NF-κB. These components are being explored intensively to control the pathogenesis of DR [50,56]. The AT-I receptor antagonist valsartan and the AT-II receptor antagonist PD123319 attenuated the increase in retinal VEGF expression observed in diabetic rats [57]. A proteomics analysis revealed that the differential expression of certain proteins in the retina of diabetic mice was controlled by treatment with candesartan, an AT-1 blocker [58]. Other inhibitors of AT-I (e.g., losartan and candesartan cilexetil) are undergoing clinical trials for the management of dysregulated RAS in DR [59,60].

The blockade of the RAS at the level of ACE inhibition or angiotensin reduces the increase in retinal VEGF and VEGFR-2 that occurs in diabetic rats and transgenic rats with oxygen-induced retinopathy (OIR) and attenuates vascular pathology, including the proliferation of endothelial cells, vascular leakage, angiogenesis, and inflammation [61,62]. The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus Study (EUCLID) has shown the beneficial effect of lisinopril in reducing the risk of DR progression in diabetic patients [63]. Recent work by Zheng et al. has shown the therapeutic effect of the ACE inhibitor perindopril on decreasing the VEGF-to-PEDF ratio [64]. However, both the UK Prospective Diabetes Study (UKPDS) and Appropriate Blood Pressure Control in Diabetes (ABCD) trials failed to show a benefit of ACE-inhibitor treatment in DR patients [30]. Therefore, specific RAS inhibitors remain to be discovered in efforts toward controlling DR.

**Antioxidants for the Management of DR**

An increased level of oxidative stress in diabetes plays an accelerated role in the progression and pathogenesis of diabetic retinopathy. Diabetes induces increased AGE formation, the activation of aldose reductase, hexosamine, the PKC pathway, altered lipoprotein metabolism, and excess levels of excitatory amino acids, all of which may lead to an increased production of reactive oxygen and nitrogen species (ROS/RNS) [65,66]. Oxidative stress creates a vicious cycle of macromolecular damage by increasing the production of more ROS/RNS, activating several metabolic pathways, which in turn dysregulate cellular and molecular mechanisms associated with DR [43,67].

Strategies to prevent the deleterious effects of oxidative stress or free radicals have been considered as potential treatments...
of this disease. However, antioxidants have not effectively con-
trolled diabetic retinopathy in clinical trials. Antioxidant ther-
apy in combination with other treatments may have a role in
slowing the progression of diabetic retinopathy. The increased
levels of VEGF in the retinas of diabetic rats were attenuated
by 2 antioxidants, alpha-lipoic acid and taurine. The admin-
istration of a mixture of antioxidants also inhibits the activa-
tion of NF-κB, which is involved in the regulation of a large
number of genes. Feeding rats a diet supplemented with se-
vral antioxidants, including alpha-tocopherol, N-acetyl cyste-
ine, ascorbic acid, and beta-carotene, inhibited the increase
of caspase 3 activity. The administration of vitamin C and vi-
tamin E prevented the inhibition of enzymes such as glutathi-
one reductase, glutathione peroxidase, superoxide dismutase,
and catalase. Clinical studies have shown that high doses of
vitamin E can apparently reverse some of the changes in ret-
inal vessels that occur in DR [68]. Benfotiamine (vitamin B1),
a lipid-soluble thiamine derivative, blocked major hyperglyce-
mia-induced pathways and prevented experimental diabetic
retinopathy [69]. A combination of oral benfotiamine and al-
pha-lipoic acid reduced AGE and ROS formation in animal stud-
ies [70]. The administration of antioxidants in a study of type
2 diabetic patients with non-PDR maintained the antioxidant
plasma status levels with decreased oxidative plasma activity
as measured by oxidative malondialdehyde (MDA) and total
antioxidant status (TAS) [71]. The use of PEDF as a therapeutic
option to block pathways that lead to the production of ROS
are being extensively studied and remain to be validated for
human use [72]. Therefore, antioxidant therapy may be use-
ful as an adjunct treatment in combination with other treat-
ments for the prevention of retinal damage.

Lipid-Lowering Drugs

There is a growing body of evidence suggesting that serum
lipid and fatty acid composition, concentration, and tissue dis-
tribution contribute to the development and severity of DR
[73]. High levels of lipids and fatty acids are associated with
increased oxidative stress, an inflammatory response, and an
altered physiological metabolic profile in the retina and vitre-
ous humor, leading to the progression of DR [74,75].

The therapeutic use of lipid-lowering drugs such as fibrates and
cholesterol-lowering drugs have been found to have a great po-
tential in the treatment of DR. Both the Early Treatment Diabetic
Retinopathy Study (ETDRS) and the Fenofibrate Intervention
and Event Lowering in Diabetes (FIELD) trial have shown the
reduced need for laser treatment in patients with DR who re-
cieved these therapies [76]. Statins, (e, 3-hydroxy-3-methylgl-
utarlyl coenzyme A [HMG-CoA] reductase inhibitors) have also
been evaluated in the treatment of DR. The combination of fe-
nofibrate with simvastatin reduced the rate of progression of
DR compared with simvastatin alone [77]. In diabetic rats, the
administration of simvastatin protected against oxidative dam-
age by scavenging free radicals and restoring the nonenzymatic
and enzymatic antioxidant systems [78]. Derivatives of polyun-
saturated fatty acids such as lipoxins possess anti-inflamma-
atory actions and suppress the production of interleukin-6, TNF-α,
and VEGF. More recently, Das [79] proposed that lipoxins could
be of significant benefit in the prevention and management of
diabetic macular edema and retinopathy. Thus, these drugs can
act as potential lipid-lowering therapeutic treatments in pre-
venting retinal complications in the management of DR [80].

Neuroprotection

Neurodegeneration is well established in the early stage of dia-
abetic retinopathy, which involves the retinal ganglion cells and
cells of the inner plexiform layers [81]. Increasing evidence sug-
gests that dysregulated level of metabolites (e.g., glutamate,
homocysteine, and branched chain amino acids) in the diabetic
retina may cause excitotoxicity to neurons. Neuroprotective
treatments have attracted significant interest as therapies for
DR, and considerable attention has been given to discovering
neuroprotective drugs/agents that could possibly repair vision
loss and damage to ganglion cells.

The intraocular administration of MK-801, an N-methyl
D-aspartate (NMDA) receptor antagonist, has been shown to
protect against neurodegenerative conditions [82]. Another
NMDA receptor antagonist demonstrated a neuroprotective ef-
fect in RGCs when exposed to glutamate [83]. In another study,
memantine treatment in animal models of diabetes exhibited
neuroprotection in addition to reduced vitreoretinal VEGF pro-
tein levels and reduced BRB breakdown [84]. Recently, Smith
et al showed that a specific sigma receptor-1 ligand, pentaz-
ocine, protected neurons in an in vivo model of retinal degen-
eration, suggesting that sigma ligand may be a potential ther-
apy for neurodegenerative diseases of the retina [85]. In one of
our studies, we found that gabapentin (Neurontin) administration
to diabetic rats reduced caspase-3 activity and reduced the
increased levels of ROS in the diabetic retina, suggesting
these agents may protect neuronal cells [86].

Neurotrophins such as brain-derived neurotrophic factor (BDNF)
are important for the survival of RGCs [87]. Several studies have
evaluated the therapeutic merits of BDNF supplied either ex-
ogenously or by injection in diabetic mice for treating neuro-
degeneration in the diabetic rat retina [88,89]. Treatment with
BDNF in combination with ciliary neurotrophic factor (CNTF)
has been shown to rescue photoreceptors in retinal explants,
conveying its neuroprotective effects [90]. Thus, neurotro-
phins could be active therapeutic agents to protect against neu-
rodegeneration in DR.
Stem Cells as a Therapeutic Option for DR

Stem cells have the potential to participate in the formation of normal-appearing intraretinal vascularization. It has been demonstrated that hematopoietic stem cells isolated from bone marrow can differentiate into all hematopoietic cell lineages, including endothelial cells, astrocytes, and retinal pigment epithelial cells, and provide a repair function [91]. One promising therapy might be the use of hematopoietic stem cells to preferentially form intraretinal capillaries. Recently, it has been reported that the intravitreal administration of hematopoietic stem cells selectively prevented blood vessel loss and promoted blood vessel growth. The feasibility and safety of transplanting mononuclear cells derived from autologous bone marrow has successfully been demonstrated in a human eye with advanced atrophy of the retina and optic nerve caused by DR [92]. Such intravitreal injection of autologous bone marrow-derived mononuclear cells in patients with retinitis pigmentosa, cone-rod dystrophy, and early DR has shown promising results in a phase I trial without any adverse effects [93]. Studies of the potential applications of stem cells are opening new avenues for maintaining normoxia and subsequently reducing the induction of retinal neovascularization, resulting in the management of DR [94].

Ribonucleic Acid (RNA) Interference (RNAi)

RNAi is a powerful tool that allows the production of double-stranded RNA molecules that can specifically inhibit the production of a particular gene product [95]. RNAi in the form of short interfering RNA (siRNA) targeting VEGF inhibited VEGF production in human RPE cells. In addition, siRNA attenuated the production of VEGF, IL-6, IL-8, TGF-β, and MCP-1 in ARPE cells [96]. HIF-1α siRNA and VEGF siRNA specifically downregulated HIF-1α and VEGF mRNA and protein levels in human umbilical vein endothelial cells (HUVECs) and in the mouse retina in an ischemic retinopathy model [97,98]. siRNAs reduced the production of angiogenic molecules in patients with macular degeneration and diabetic retinopathy [99]. The intravitreal injection of specific siRNAs targeting VEGF has been shown to prevent retinal and choroidal neovascularization in mice [100]. Bevasiranib is an siRNA against VEGF, developed by Acuity Pharmaceuticals. A Phase III, randomized, double-masked clinical trial evaluating the efficacy of bevasiranib in patients affected by wet age-related macular degeneration (AMD) was recently terminated [101]. However, results from randomized clinical trials evaluating the use of bevasiranib in the treatment of diabetic macular edema are pending. Another molecule, siRNA-027, developed by Sirna Therapeutics, was well tolerated with a single intravitreal dose in patients with choroidal neovascularization (CNV) resulting from neovascular AMD [102].

Conclusions

All of the newer drugs/strategies discussed here have been tested primarily in laboratory investigations, which may be useful in controlling disease progression if carried out at early stages of the disease in humans. However, most of these drugs are still awaiting clinical trials to demonstrate their efficacy and safety in humans. Some of these new therapeutic drugs and approaches may control the incidence and progression of DR with greater efficacy and safety. Future research may delineate several different pathways, and specific therapies will likely target the master regulatory molecules or pathways involved in DR.

Acknowledgement

The authors acknowledge funding from the Deanship of Scientific Research (RGP-VPP-052) at King Saud University.

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