Chapter 5
The Kallikrein-Kinin System in Diabetic Retinopathy

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Abstract Diabetic retinopathy (DR) is a major microvascular complication associated with type 1 and type 2 diabetes mellitus, which can lead to visual impairment and blindness. Current treatment strategies for DR are mostly limited to laser therapies, steroids, and anti-VEGF agents, which are often associated with unwanted side effects leading to further complications. Recent evidence suggests that kinins play a primary role in the development of DR through enhanced vascular permeability, leukocytes infiltration, and other inflammatory mechanisms. These deleterious effects are mediated by kinin B1 and B2 receptors, which are expressed in diabetic human and rodent retina. Importantly, kinin B1 receptor is virtually absent in sane tissue, yet it is induced and upregulated in diabetic retina. These peptides belong to the kallikrein-kinin system (KKS), which contains two separate and independent pathways of regulated serine proteases, namely plasma kallikrein (PK) and tissue kallikrein (TK) that are involved in the biosynthesis of bradykinin (BK) and kallidin (Lys-BK), respectively. Hence, ocular inhibition of kallikreins or antagonism of kinin receptors offers new therapeutic avenues in the treatment and management of DR. Herein, we present an overview of the principal features and known inflammatory mechanisms associated with DR along with the current therapeutic approaches and put special emphasis on the KKS as a new and promising therapeutic target due to its link with key pathways directly associated with the development of DR.

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Abbreviations

ACE	Angiotensin-converting enzyme
AGE	Advanced glycation end products
BRB	Blood–retinal barrier
BK	Bradykinin
B1R	Bradykinin receptor 1
B2R	Bradykinin receptor 2
C1-INH	Complement 1 inhibitor
Cox-2	Cyclooxygenase-2
DME	Diabetic macular edema
DR	Diabetic retinopathy
eNOS	Endothelial nitric oxide synthase
FXII	Factor XII
HMWK	High molecular weight kininogen
HIF-1	Hypoxia inducible factor-1
iNOS	Inducible nitric oxide synthase
IL-1 β	Interleukin-1 beta
ICAM-1	Intercellular adhesion molecule1
IGF	Insulin-like growth factor
KKS	Kallikrein-kinin system
LMWK	Low molecular weight kininogen
NFk-B	Transcriptional nuclear factor-kappa B
PLA_2	Phospholipase A_2
PK	Plasma kallikrein
PPK	Plasma prekallikrein
PKC	Protein kinase C
ROS	Reactive oxygen species
NO	Nitric oxide
NPDR	Nonproliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
RAS	Renin–angiotensin system
STZ	Streptozotocin
$O_2^{\bullet -}$	Superoxide anion
TK	Tissue kallikrein
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
VEGFR-1	Vascular endothelial growth factor receptor 1
VEGFR-2	Vascular endothelial growth factor receptor 2

5.1 Introduction

Diabetic retinopathy (DR) is a major microvascular complication of prolonged diabetes mellitus (DM) and hyperglycemia. It results in severe retina damage causing blindness. Approximately 10 % of diabetic patients develop severe visual impairment, and about 2 % lose their vision after 15 years of DR incidence. According to the World Health Organization, more than 382 million people are currently affected by diabetes worldwide and this number is on rise given the aging of the population. DR is thus a major cause of vision loss among the working age adults (20–65 years old) in industrialized countries. The current therapies against DR are limited by uncomfortable and repetitive procedures (repetitive intravitreal drug injections, panretinal photocoagulation, vitrectomy, etc.) associated with risk of endophthalmitis and damage to the sane neural retina. For these reasons, new pharmacological targets based on the understanding of the pathophysiological mechanisms of the disease are needed to elaborate safe and comfortable therapeutic approaches for DR treatment. As we will discuss in this review, the kallikrein-kinin system (KKS) is a promising therapeutic target due to its link with key pathways directly associated with the development of DR.

5.2 Diabetic Retinopathy

DR is primarily considered as a vascular disease with leaky and occluded blood vessels; however, neuroretina damage also contributes to the etiology of DR and visual impairment of patients (Antonetti et al. 2006). The pathological hallmarks of DR resulting in blindness are linked to the deregulation of key intracellular pathways related to oxidative stress and inflammation.

5.2.1 Pathological Hallmarks Linked to Vision Loss

Dilation, tortuosity, and branching of the blood vessels as well as aneurisms, hemorrhages, exsudative deposits, commonly named cotton–wool spots, and neovessels are seen in the fundus of DR patients (Fig. 5.1) (Frank 2004). Angiography examination further shows vascular leakage of plasma into the central portion of the retina leading to subsequent diabetic macular edema (DME). As observed by ocular coherent tomography, swelling of the retina during DME results in a severe retinal detachment (Fig. 5.1c). Proteomic analyses of vitreous fluid obtained from patients with advanced DR also reveal abundant quantities of intracellular red blood cell proteins, including hemoglobin and carbonic anhydrase1 (Gao et al. 2007), suggesting that intraocular bleeding markedly alters the vitreous proteome. In certain patients, the electroretinogram is affected in early

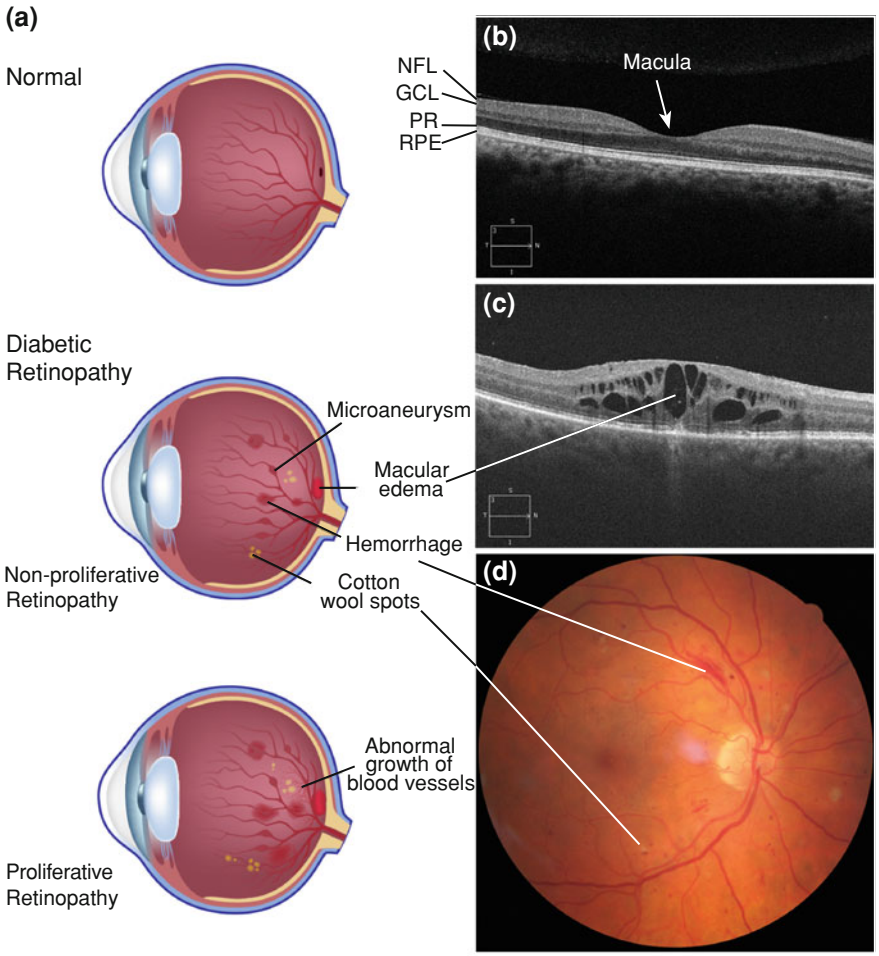


Fig. 5.1 Pathological changes within the retina of diabetic patients. **a** Schematic representations of pathological changes occurring in the retina during nonproliferative diabetic retinopathy (*middle panel*) and proliferative retinopathy (*bottom panel*) compared to sane eye (*upper panel*). Pathological features, such as macular edema, hemorrhage, microaneurysm, and exudates accumulation (cotton wool spot), occur consistently at each developmental stage and develop during the course of the disease. **b** Ocular coherent tomography capture of a sane retina showing the macula and the different layers of the retina. *NFL* nerve fiber layers, *GCL* ganglion cells layer, *PR* Photoreceptor, and *RPE* retinal pigmented epithelium. **c** Ocular coherent tomography capture of a diabetic retina showing the macular edema. **d** Fundus photograph of an eye featuring major NPDR complications. Images in (**a**) have been acquired from Shutterstock http://www.shutterstock.com; ocular coherent tomography captures (**b**, **c**) have been kindly provided by Dr Sebastien Olivier (Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada)

stages of the disease as β wave and oscillatory potentials are decreased and delayed (Bearse et al. 2004), suggesting death and apoptosis of diverse retinal cells including photoreceptors (Aizu et al. 2002; Park et al. 2003), and retinal ganglion

cells (Chihara et al. 1993). The glial cells—Müller cells and astrocytes—are also affected, which reduces the metabolic supply of the neurons and induces the production of pro-inflammatory cytokines (Lieth et al. 2000).

DME and neovascularization are the major pathological hallmarks of DR leading to blindness. DME, an early process in the development of DR, induces a loss of visual acuity through thickening of the retina. DME affects 25 % of the diabetic patients (Antonetti et al. 2012), and its incidence is 11 % in type 1 and 14 % in type 2 diabetic patients ten years after the onset of the disease (Klein and Moss 1995; Romero-Aroca et al. 2011). Neovascularization, occurring in the most severe forms of the disease, produces cloudy vision through obstruction of the light paths by the neovessels and vision loss through traction retinal detachment (Fong et al. 2004).

5.2.2 Progression of the Disease

The progression of DR is very slow, yet it is predictable as significant pathological features occur consistently at each developmental stage and during the course of the disease (Wilkinson-Berka 2006). DR progresses from initial mild nonproliferative abnormalities characterized by hyperglycemia-induced intramural pericytes death and thickening of the basement membrane of blood vessels leading to blood flow changes and leakage of blood–retinal barrier (BRB) (Chakrabarti et al. 2000; Cheung et al. 2010). The dysfunction of the vascular endothelium and the altered micro- and macro-vascular permeability produce microangiopathy complications (El-Asrar 2012), such as microaneurysms, microhemorrhages, and ischemic areas. Thus, incidence and severity of hemorrhage and DME often increase with DR progression. These early signs of vascular changes are followed by moderate and severe nonproliferative diabetic retinopathy (NPDR), where vascular closure occurs. Severe NPDR then enters into an advanced or proliferative diabetic retinopathy (PDR) stage involving growth of new blood vessels and fibrosis of the retina and posterior surfaces of the vitreous. Intraretinal hemorrhage can occur at all stages of the DR and has been attributed to rupture of retinal vessels (Frank 2004). In addition, preretinal and vitreous hemorrhage can occur from newly formed fragile vessels generated during PDR. Retinal and vitreous hemorrhage can lead to blurred vision, spots, lines, or streaks in the field of vision.

5.2.3 Blood Flow Changes in Diabetic Retinopathy

In DR patients, blood flow alteration occurs in the early stage of retinopathy, sometimes before the apparition of pathological features. Nevertheless, there is no clear picture of blood flow changes, possibly because of the diversity of the techniques used. Most studies show vasodilation and decrease in red blood cell

velocity (Feke et al. 1985; Grunwald et al. 1986, 1992; Patel et al. 1992). However, some studies show decrease in blood flow in type 1 diabetic patients without sign of retinopathy (Bursell et al. 1996), decrease in blood flow in early phase of DR, yet increase in blood flow in more advanced DR (Clermont et al. 1997). Other studies have shown no change or increase in blood flow in the early stage and a decrease in blood perfusion in the PDR stage (Kohner et al. 1975; Cunha-Vaz et al. 1978a, b; Blair et al. 1982; Yoshida et al. 1983). Similar discrepancies in blood flow changes are also observed across different time point and diabetic animal models (Pugliese et al. 1990; Sutera et al. 1992; Tilton et al. 1989; Bursell et al. 1992; Clermont et al. 1994, 1997; Takagi et al. 1995, 1996; Higashi et al. 1998; Miyamoto et al. 1996; Pouliot et al. 2011).

5.2.4 Pathological Mechanisms

Although the exact mechanism by which diabetes causes retinopathy remains unclear, several studies have shown the elevation of reactive oxygen species (ROS), advanced glycation end products (AGE), and circulating and vitreous cytokines and chemokines. This triggers an inflammatory response in retinal vasculature and subsequent endothelial dysfunction, i.e., increased vascular permeability, leukostasis, and blood flow deregulation (Kowluru et al. 2012). Hence, different pathways are involved in the development of retinopathy, such as polyol pathway also known as aldose reductase/sorbitol pathway, protein kinase C (PKC) activation, oxidative stress, renin–angiotensin system (RAS), carbonic anhydrase, retinal apoptosis, and growth factors (Fig. 5.2) (Tarr et al. 2013). Small blood vessels are especially vulnerable to the overaccumulation of glucose and/or fructose. As the disease progresses, the lack of oxygen induces hypoxia accelerating retinal ganglion cells death and consequently irreversible loss of vision (Frank 2004).

The accumulation of glucose favors the glucose flux through the polyol pathway leading to conversion of glucose into sorbitol and fructose. This initiates vascular damage via the oxidative stress from ROS (Mara and Oates 2008), which damages DNA, lipids, and proteins (Rosen and Spiegelman 2001; Kowluru et al. 2012; Madsen-Bouterse and Kowluru 2008) but also from AGE products (Milne and Brownstein 2011). The retina is the most metabolically active tissue in the human body and, therefore, is highly sensitive to reductions in oxygen levels. Overexpression of NAD(P)H oxidase is shown in early diabetes and might contribute to increase the formation of superoxide anion ($O_2^{\bullet -}$). The formation of $O_2^{\bullet -}$ can also result from mitochondria and the uncoupling of endothelial nitric oxide synthase (eNOS). $O_2^{\bullet -}$ reacts immediately with NO to generate peroxynitrite $ONOO^-$, a highly toxic molecule. NO being strongly vasodilator, its reduced bioavailability results in altered vascular tone and endothelial dysfunction (Kowluru and Chan 2007).

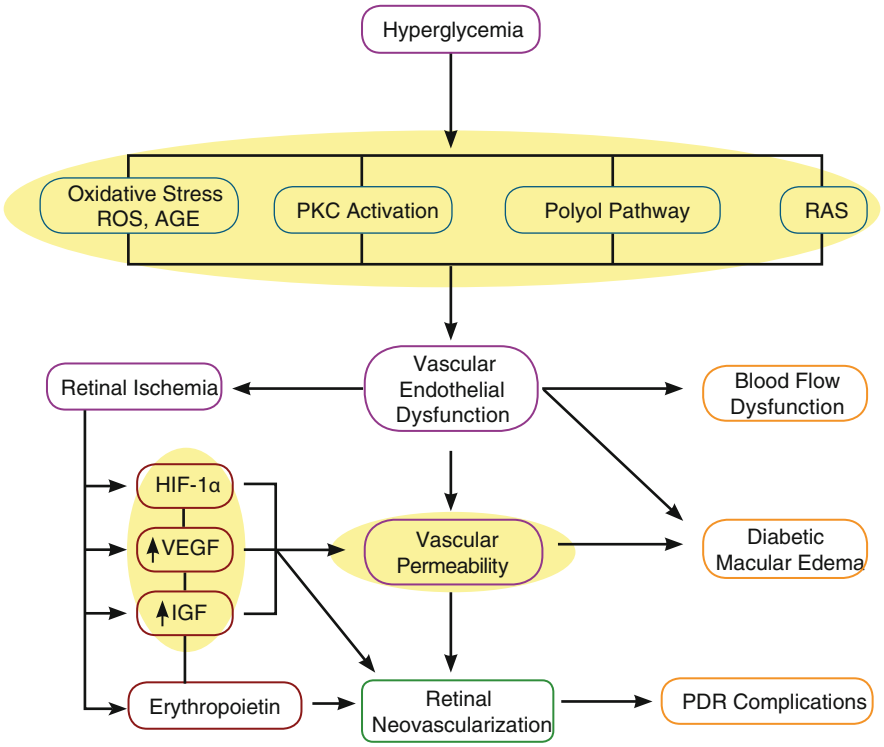


Fig. 5.2 Biochemical pathways contributing to diabetic retinopathy pathophysiology. The early onset of inflammatory changes in the vasculature plays an important role in endothelial dysfunction, i.e., increased vascular permeability, leading to macular edema, blood flow deregulation, and neovascularization (see text for details). *Yellow shadows* underline the target of kallikrein-kinin system actions. *AGE* advanced glycation end products, *HIF-1α* hypoxia-inducible factor 1, *IGF* insulin-like growth factor, *PDR* proliferative diabetic retinopathy, *PKC* protein kinase C, *ROS* reactive oxygen species, *RAS* renin–angiotensin system, and *VEGF-α* vascular endothelial growth factor

VEGF-A and its receptors VEGF-R1 and VEGF-R2 are consistently upregulated in the diabetic retina, including in humans (Aiello et al. 1994; Adamis et al. 1994; Pouliot et al. 2012). VEGF overexpression has been related to hyperglycemia, oxidative stress (Sone et al. 1997; Kuroki et al. 1996), and hypoxia, particularly to high levels of the hypoxia-inducible factor-1 (Aiello et al. 1995; Ikeda et al. 2006). Overexpression of VEGF mainly occurs in retinal ganglion cells and Müller cells (Famiglietti et al. 2003), and it enhances the expression of ICAM1, vascular permeability, DME, and vessel tortuosities (Tolentino et al. 1996; Qaum et al. 2001; Joussen et al. 2002b; Pouliot et al. 2012). VEGF induces proliferation of vascular endothelial cells (Aiello et al. 1994), and its inhibition reduces retinal neovascularization (Bainbridge et al. 2002). Furthermore, insulin-like growth factor (IGF-1) is increased in the vitreous of patients with DR (Inokuchi et al. 2001) and in diabetic

animal models (Ruberte et al. 2013). The expression of erythropoietin, another growth factor strongly regulated by hypoxia, is enhanced in the neuroretina and the vitreous of diabetic patients (Chung et al. 2009; Garcia-Ramirez et al. 2008) and can account for neovascularization.

5.2.4.1 Inflammation: Leukostasis and Vascular Hyperpermeability

Inflammation of the retina is a major early pathological hallmark of DR. Diverse inflammatory and vasodilator factors are expressed and modify endothelial function. This causes deregulation of blood supply and enhanced vascular permeability and leukocytes infiltration in the retina.

Inflammatory Mediators

Hyperglycemia-induced oxidative stress activates the transcriptional nuclear factor-kappa B (NF-κB), which in turn enhances the expression of pro-inflammatory genes, notably cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukin-1 beta (IL-1β), and tumoral necrosis factor (TNF-α) (Kern 2007). The enhanced expression of TNF-α and IL-1β in the diabetic retina (Joussen et al. 2002a; Vincent and Mohr 2007; Kowluru and Odenbach 2004; Krady et al. 2005) causes leukostasis, apoptosis, adhesion molecules formation, and cytokine formation. The selective inhibition of TNF-α significantly reduces the intercellular adhesion molecule-1 expression, which is responsible for leukocytes adhesion to the vessel wall capillary occlusion, endothelial cell injury and death, and vascular hyperpermeability (Joussen et al. 2002a). IL-1β contributes to the degeneration of endothelial cells and retina capillaries through caspase-1 activation (Kowluru and Odenbach 2004; Vincent and Mohr 2007). Moreover, iNOS is overexpressed in the diabetic retina and results in the overproduction of NO (Abu El-Asrar et al. 2001; Du et al. 2004). In iNOS knockout mice, leukostasis, degeneration of endothelial cells and retina capillaries, and production of $O_2^{\bullet -}$ are reduced (Zheng et al. 2007). COX-2 is an inducible enzyme found on macrophages in inflammation loci (Harris et al. 2001; Yermakova and O'Banion 2000). Like other COX isoforms, it mediates the production of vasoactive prostaglandin and thromboxane A2. COX-2 expression and production of prostaglandins are increased in the retina of diabetic rats (Du et al. 2004; Ayalasomayajula and Kompella 2003; Naveh-Floman et al. 1984; Johnson et al. 1999). Prostaglandin E2 production is significantly diminished in the streptozotocin (STZ) rat retina by celecoxib, a selective inhibitor of COX-2, but not by SC560, a selective inhibitor of COX-1, suggesting a predominant involvement of COX-2 in this process (Ayalasomayajula et al. 2004). In addition, COX-2 inhibition decreases vascular hyperpermeability and leukostasis in STZ diabetic rat and endothelial cell death induced by high glucose concentration in vitro (Joussen et al. 2002b; Ayalasomayajula and Kompella 2003; Du et al. 2004).

Leukostasis

Inflammation and enhanced expression of adhesion molecules in retina promote leukostasis in which circulating leukocytes adhere to endothelial cells of inflamed vessels, roll and transmigrate into the tissue (Crane and Liversidge 2008). The number of leukocytes is increased in retinal vessels and tissue of diabetic patients and animal models (McLeod et al. 1995; Miyamoto et al. 1998, 1999; Joussen et al. 2004; Pouliot et al. 2012). In the tissue, leukocytes promote inflammatory responses, including phagocytosis of foreign particles, production of antibodies, and secretion of inflammatory factors. The adhesion of leukocytes to the vessel walls might also contribute to the endothelial cell death, alteration of microcirculation (Kern 2007; Joussen et al. 2001), and increased vascular permeability (Del Mashio et al. 1996).

Vascular Permeability

In the eyes, the BRB plays an important role in retinal homeostasis by controlling the passage of macromolecules in the intima of large vessels. An intact endothelium also selectively modulates the transfer of albumin, fluid, and small solutes from the vascular to the interstitial fluid compartment of different capillary networks. Tissue edema due to leakage of BRB and alteration in the passage of substrates/waste products between the vascular and interstitial volumes lead to selective organ damage and development of morbid conditions (Auckland and Reed 1993). BRB undergoes breakdown during diabetes, related to inflammatory cytokines and growth factors such as VEGF (Kern et al. 2007; Hawkins and Davis 2005; Bates and Harper 2002). The increase in vascular permeability is also associated with changes in adhesion molecules such as ICAM-1 (Joussen et al. 2002a) or intercellular junctions such as occludine and tight junction protein ZO-1 (Antonetti et al. 1998; Barber et al. 2000; Leal et al. 2007).

5.2.5 Clinical Management of Diabetic Retinopathy

Many medical advances for the treatment of DR have been postulated and investigated with long-term clinical studies in large cohorts of diabetic patients (Simo and Hernandez 2009). Before any specific treatment, controlling glycosylated hemoglobin levels at less than 7 % to prevent or minimize retinopathy complications should be a primary goal (Rodriguez-Fontal et al. 2009; Liew et al. 2009). Although controlling blood glucose levels is essential in preventing or controlling the progression of the disease, there is always a necessity for medication in treating the advancement of retinopathy. Surgery and pharmacological treatments are currently used to treat NPDR and PDR.

In panretinal photocoagulation, the standard care for PDR complications (Bhavsar 2006; Network 2008), 500-μm-size laser-lesion spots are made throughout the whole extent of the damaged retina. The underlying principles are (1) to destroy the hypoxic retina, and in turn decrease the production of VEGF, and (2) to increase the diffusion of oxygen from the choroid, which supplements retinal circulation (Lock and Fong 2011). Instead of laser surgery, vitrectomy is another surgical treatment option used to restore the vision in advanced PDR patients with long-standing vitreous hemorrhages, traction retinal detachment, and combined traction/rhegmatogenous retinal detachments (Joussen and Joeres 2007). Vitreo-retinal surgery is however a complicated treatment that should be carried out only by vitreoretinal specialists.

Diverse pharmaceutical agents have been used for the treatment of DR. Some therapies to prevent vascular complications like thrombosis or hemorrhages have been initiated regarding their beneficial effects on DR but were never used for the treatment on large scale such as (1) Aspirin, used till 1998 but discontinued because it was non-effective to prevent long-term progression of DR (Akduman and Olk 1998; Bhavsar 2006), (2) ovine hyaluronidase (Vitrase, Bausch and Lomb) for the clearance of severe vitreous hemorrhage (Bhavsar et al. 2008), (3) candesartan (angiotensin AT1 receptor antagonist) used commonly for the treatment of hypertension (Chaturvedi et al. 2008), (4) lisinopril, the angiotensin-converting enzyme (ACE) inhibitor (Chaturvedi et al. 1998), (5) fenofibrate (PPAR-α agonist) (Keech et al. 2007), and (6) triamcinolone, intravitreal corticosteroid therapy for the treatment of DME during NPDR and PDR. Triamcinolone is commonly used; however, its effect is transient and lasts around three months; therefore, reinjections are needed. Currently, the blockade of VEGF is the most popular pharmaceutical therapy showing significant improvement of the vision by reducing vascular hyperpermeability and neovascularization in DME and PDR (Michaelides et al. 2010; Simo et al. 2006; Wirostko et al. 2008; Arevalo and Garcia-Amaris 2009; Rodriguez-Fontal et al. 2009). Nowadays, four anti-VEGF agents directed against different variants of the VEGF protein family are commonly used: Pegaptanib sodium, Ranibizumab (Lucentis, Novartis), Bevacizumab (Avastin; Genen-tech), and Aflibercept (Regeneron Pharmaceuticals/Sanofi-Aventis), the last generation of anti-VEGF drugs that target all human forms of VEGF with a total molecular weight of 115 kDa. All these anti-VEGF drugs need to be intravitreally injected every month, which increases the risk of substantial adverse effects such as infection, cataract formation, glaucoma, and vision loss in some cases (Mohamed et al. 2007). Specifically, their size raised a concern for the possible physical obstruction of the trabecular meshwork and the triggering of immune responses. Studies have investigated the number of injections as a risk factor for sustained intraocular pressure elevation (Hoang et al. 2012; Tseng et al. 2012) and changes in the vessel diameter (Fontaine et al. 2011).

5.3 Involvement of the Kallikrein-Kinin System in Diabetic Retinopathy and its Treatment

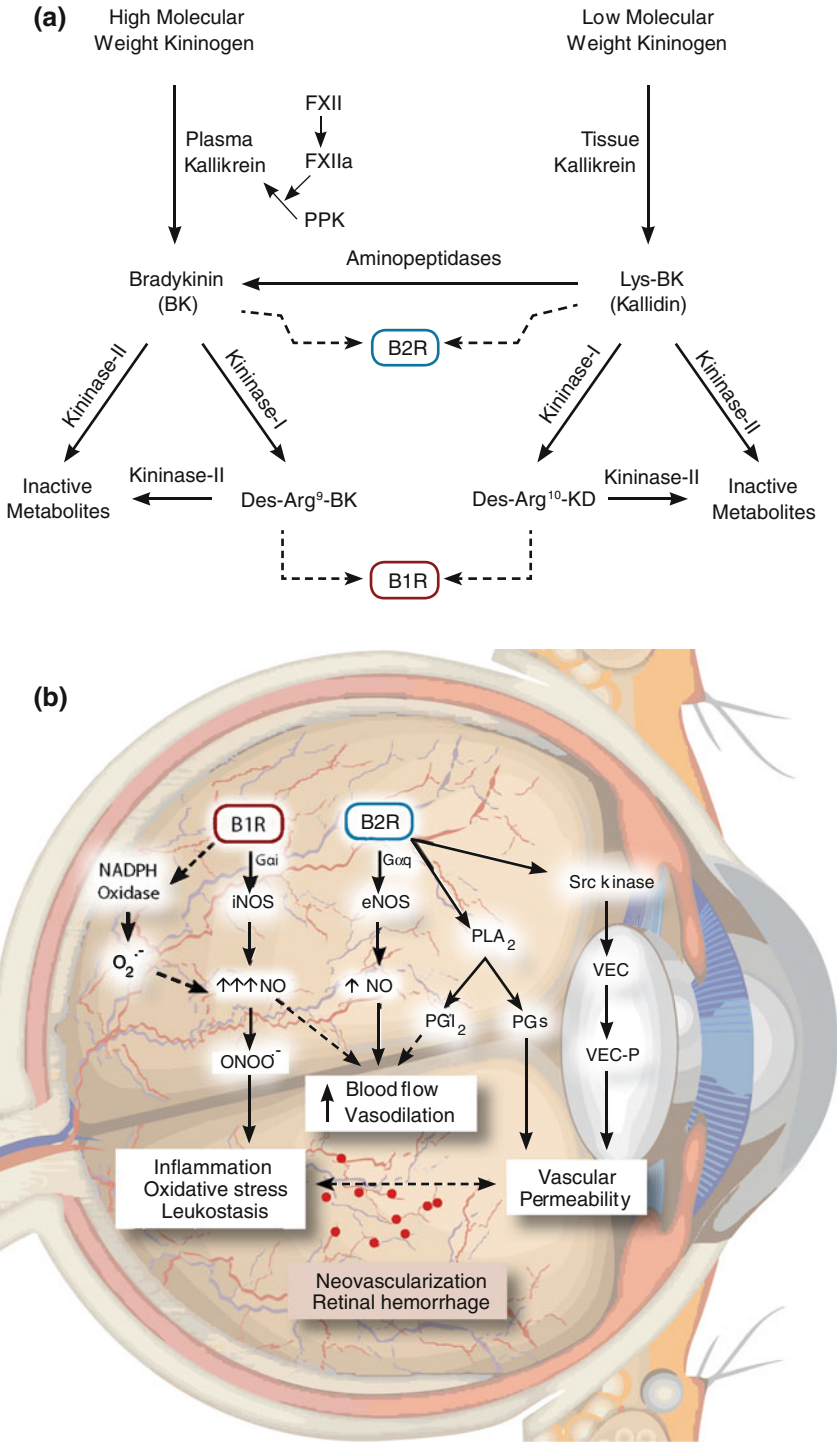
As mentioned above, current therapies against PDR are limited by uncomfortable methods, which increase risks of endophthalmitis and damage to the sane neural retina. It would be an asset to develop topical administration of pharmaceutical agents for chronic treatment of DR. We have previously shown in the rat that topical administration of a drug targeting the KKS was effective to reverse deregulation of key pathways directly associated with the development of DR (Pouliot et al. 2012). More extensively, different KKS components could be targeted to prevent retinal complication of diabetes as they exert vasoactive, angiogenic, and pro-inflammatory actions and they are primary factors released in damaged tissue (Marceau et al. 1998; Couture et al. 2001). Studies have confirmed the presence of those components of KKS in the vitreous and retina of people with DR (Phipps et al. 2008; Liu and Feener 2013).

5.3.1 The Kallikrein-Kinin System

KKS is a complex and multifunctional endogenous peptidergic system involved in the release of vasoactive kinins (Fig. 5.3). Kinins are implicated in various physiological and pathological processes (Moreau et al. 2005; Regoli et al. 2012), while they exert a dual role in physiopathology, namely the beneficial protection of the endothelium and their involvement in inflammatory processes (Blaes and Girolami 2013).

5.3.1.1 Synthesis and Degradation of Kinins

Kinins are small polypeptides (BK and Lys-BK also named kallidin) synthesized from their precursors, high molecular weight kininogen (HMWK), and low molecular weight kininogen (LMWK) under the action of serine proteases named tissue kallikrein (TK) and plasma kallikreins (PK) (Fig. 5.3a). PK is a single gene product produced primarily in the liver and secreted as the proenzyme prekallikrein (PPK), one of the most abundant protease zymogens in blood. PPK undergoes activation to PK by factor XII (FXII) following interactions with negatively charged surfaces (Schmaier and McCrae 2007), activated platelets (Muller et al. 2009), mast cells (Oschatz et al. 2011), and misfolded proteins (Maas et al. 2008). PK mostly circulates (75 %) as a complex with HMWK and is activated by a modest increase in pH induced by extracellular carbonic anhydrase (Bjorkqvist et al. 2013). It triggers the synthesis of BK. The primary physiological inhibitors of PK are complement 1 inhibitor (C1-INH) and complement α-2 macroglobulin (Joseph and Kaplan 2005). TK belongs to a family of 15 genes (Webb 2011) and


(a)
High Molecular Weight Kininogen
Low Molecular Weight Kininogen
FXII
FXIIa
PPK
Plasma Kallikrein
Tissue Kallikrein
Aminopeptidases
Bradykinin (BK)
Lys-BK (Kallidin)
B2R
Kininase-II
Kininase-I
Kininase-I
Kininase-II
Inactive Metabolites
Kininase-II
Des-Arg9-BK
Des-Arg10-KD
Kininase-II
Inactive Metabolites
B1R
(b)
B1R
B2R
Gαi
Gαq
NADPH Oxidase
iNOS
eNOS
Src kinase
PLA2
O2.-
↑↑↑NO
↑ NO
VEC
PGI2
PGs
VEC-P
ONOO-
Blood flow Vasodilation
Inflammation Oxidative stress Leukostasis
Vascular Permeability
Neovascularization Retinal hemorrhage

◀**Fig. 5.3** Involvement of the kallikrein-kinin system in diabetic retinopathy. **a** Biosynthesis and degradation pathways of the kallikrein-kinin system (see text for details). *BK* Bradykinin, *FXII* Factor XII, Lys-BK, *KD* kallidin, *B1R* bradykinin receptor 1, *B2R* bradykinin receptor 2, and *PPK* plasma prekallikrein. **b** Proposed signaling pathways activated through B1R and B2R known to regulate pathological changes during diabetic retinopathy such as increased blood flow and vasodilation, vascular permeability and inflammation, oxidative stress, leukostasis, and the outcome neovascularization and retinal hemorrhage. *eNOS* endothelial nitric oxide synthase, *Gαi* G-protein alpha subunit i, *Gαq* G-protein alpha subunit q, *iNOS* inducible nitric oxide synthase, *PGs* prostaglandins, *PGI2* prostacyclin, *PLA2* phospholipase A2, *NO* nitric oxide, $O_2^{\bullet -}$ superoxide anion, $ONOO^{\bullet -}$ peroxynitrite, *VEC* vascular endothelial cadherin, and *VEC-P* phosphorylated vascular endothelial cadherin

generates kallidin from LMWK although HMWK also contributes in the process (Cyr et al. 2001). The production of kinins by TK is inhibited by protease inhibitors, such as kallistatin (Madeddu et al. 2007). Kallidin can be converted to BK by aminopeptidases. BK and kallidin are the endogenous ligands of the B2 receptor (B2R) and can be further converted by carboxypeptidases of the M type and the N type into active metabolites devoid of the C-terminal arginyl residue (des-Arg^9-BK and Lys-des-Arg^9-BK), which act as potent agonists of the B1 receptor (B1R) (Regoli et al. 1989; Stone et al. 2009) (Fig. 5.3a). This receptor is one of the rare G-protein-coupled receptors (GPCR), which is inducible by inflammatory mediators, in contrast to the B2R, which is constitutively expressed in multiple cell types (Leeb-Lundberg et al. 2005). Kininase II (ACE) catabolizes kinins into inactive fragments (Bader 2009).

5.3.1.2 Kinin Receptors

The B2R is constitutively expressed in all cell types and mediates most physiological effects of kinins. This classical GPCR is rapidly desensitized and internalized upon agonist stimulation (Leeb-Lundberg et al. 2005). On the other hand, the B1R is generally absent in normal physiological situation, yet it is highly inducible and overexpressed following tissue injury, inflammation, and after exposure to agents like bacterial endotoxins and pro-inflammatory cytokines, growth factors, and oxidative stress (Marceau 1995; Marceau et al. 1998; Couture and Girolami 2004; Lungu et al. 2007). Cytokine-induced B1R expression is controlled by MAP kinase and NF-κB (Larrivee et al. 1998; Ni et al. 1998; Campos et al. 1999). Because B1R is neither desensitized nor internalized, but upregulated by its own agonist, it is rather involved in chronic inflammation (Couture et al. 2001; Leeb-Lundberg et al. 2005; McLean et al. 2000; Prado et al. 2002). Various G proteins are coupled to kinin B1 and B2 receptors depending on the cell type. The most common signaling pathway involves Gq with the subsequent activation of phospholipase C and the production of inositol-1-4-5-triphosphate and diacylglycerol, which lead to the release of intracellular calcium and the activation of PKC, respectively (Blaes and Girolami 2013). In endothelial cells, Ca^{2+} stimulates eNOS and phospholipase A2 (PLA_2) resulting in the production of NO and prostaglandins (Fig. 5.3b). The B1R is also associated

with Gi and the ERK cascade of signalization, which is linked to the activation of the iNOS and the subsequent formation of large amount of NO (Brovkovych et al. 2011). This can cause further inflammation through the production of peroxynitrite (Fig. 5.3b). Kinin receptors are also associated with Gs and Gi to regulate adenylate cyclase and AMPc production. Kinin receptors may also activate MAP kinases and JAK/STAT pathways, involved in gene regulation (Marceau et al. 1998; Moreau et al. 2005).

5.3.2 The Kallikrein-Kinin System in the Sane and Diabetic Retina

5.3.2.1 Kallikreins

The presence of PK and HMWK has been shown in the rat retina (Takeda et al. 1999; Phipps et al. 2008). The blood levels of PPK are 16 % higher in people with diabetes than in control patients and 50 % higher in PDR patients, which indicate a systemic role of KKS in exacerbating DR (Kedzierska et al. 2005). The presence of contact system proteins, including PK, FXII, and HMWK, was detected in vitreous fluid from PDR patients, suggesting a role of PK in regulating the intraocular KKS in DR (Gao et al. 2007). Later, it was proposed that these proteins reach the retinal interstitium and vitreous by crossing the BRB through increased vascular permeability and retinal hemorrhage, because of their abundant presence in the plasma (Phipps et al. 2008). PK has also been shown to mediate plasminogen activation to plasmin (Selvarajan et al. 2001), which mediates both fibrinolysis and the activation of matrix metallo-proteinases; these findings suggest that KKS may also exert effects on vascular homeostasis through BK receptor-independent mechanisms. The presence of TK mRNA and LMWK in different cell types in the human retina has been detected (Ma et al. 1996), but its role in retinal physiology is still unknown. Kallikrein-like enzymatic activities are also found in the tissue homogenates of rabbit and swine eyes (Kuznetsova et al. 1991; Pinna et al. 2004). Nevertheless, there is evidence supporting the involvement of TK in diabetic animal models, where kallikrein is elevated in retinal tissues of diabetic rats as compared to control (Catanzaro et al. 2010). Since kallikrein binding protein levels are decreased in the diabetic retina, this may suggest better bioavailability of kallikrein in the eye (Hatcher et al. 1997).

5.3.2.2 Kinin Receptors

B2R stimulates eNOS and PLA_2 leading to the increased production of NO and prostacyclin, two potent vasodilator mediators (Fig. 5.3b). Prostaglandins generated by B2R-induced PLA2 activation may also contribute to the pathological

features of DR (Ma et al. 1996). Consistently, topical treatment with nepafenac (a COX-2 inhibitor) reduces inflammation in diabetic retina (Kern 2007). Even though eNOS is generally considered vasoprotective, activation of this pathway can exert adverse effects in neurovascular tissues (Bucci et al. 2005). B2R also activates the Src kinases and subsequently activating vascular endothelial cadherin phosphorylation, which leads to the reversible opening of the endothelial cell junctions and plasma leakage (Orsenigo et al. 2012). The concomitant activation of iNOS by B1R can cause peroxynitrite formation contributing to oxidative stress and leukostasis in the inflammatory diabetic retina (Shigematsu et al. 2002). Recent studies have shown that the B1R is upregulated early in the rat diabetic retina through a mechanism involving the oxidative stress (Abdouh et al. 2008; Pouliot et al. 2011), and its activation mediates vasodilation of retinal microvessels (Abdouh et al. 2003). Reciprocally, the activation of B1R can enhance the oxidative stress via NAD(P)H oxidase, causing the increase in its own expression and that of pro-inflammatory mediators through the NF-κB pathway in diabetic vasculature (Dias et al. 2010) (Fig. 5.3b). Hence, B1R activation can amplify and perpetuate the oxidative stress and the pro-inflammatory process through a positive feedback loop mechanism. This scenario may explain vascular permeability changes, the infiltration of leukocytes, and the upregulation of several pro-inflammatory genes in the retina of type 1 diabetic rats (Pouliot et al. 2011, 2012). This is consistent with the role of B1R in the cellular inflammatory response (McLean et al. 2000; Duchene et al. 2007). Infiltration of leukocytes is facilitated by the fact that B1R, PK, and kininogens are present at the surface of macrophages, neutrophils, and endothelial cells (Bockmann and Paegelow 2000; Bhoola et al. 2001; Araujo et al. 2001). B1R-induced infiltration of leukocytes would also be facilitated by enhanced vascular permeability associated with B1R overexpression. This is in agreement with increased susceptibility to edema in mice overexpressing B1R (Ni et al. 2003) versus B1R knockout mice, which are resistant to inflammatory edema (Pesquero et al. 2000).

B1R is expressed from 4 days up to 6 weeks after the onset of diabetes (Abdouh et al. 2003; Pouliot et al. 2011). If B1R is a biomarker of inflammatory and oxidative processes, then retina undergoes a stress from the beginning of the hyperglycemia, which persists as long as hyperglycemia is maintained. Increased mRNA expression of B1R and B2R has been found in the endothelial cells of human retinal blood vessels (Ma et al. 1996). However, this study also suggests the occurrence of B1R in the retina of healthy humans raising the concern that B1R could be induced in *post mortem* retina. To address this important issue, we have measured by quantitative RT-PCR (Table 5.1, Fig. 5.4) the expression of B1R in retina (*Eye Bank for Sight Restoration*, New York, USA) of non-diabetic and diabetic patients (56–70 years). The samples were collected after *postmortem* delay less than 10 h (Table 5.2). Our data showed marked expression of B1R mRNA levels in the retina of type 1 and type 2 diabetic donors and no detectable values in the retina of control donors (Fig. 5.4). This provides a proof of concept that B1R is present in type 1 and type 2 diabetic human retina and targeting this receptor has a clinical relevance.

Table 5.1 Sequence of primers used for qRT-PCR analyses of the patients' retina

	Sequence		Position	GenBank
B1R	Forward	5′ AAA TGC TAC GGC CTG TGA CAA TGC 3′	189–212	BC034705
	Reverse	5′ AGA TTT CTG CCA CGT TCA GTT GCC 3′	349–326	
ß-actin	Forward	5′ ACC AAC TGG GAC GAC ATG GAG AAA 3′	363–385	NM001101
	Reverse	5′ TAG CAC AGC CTG GAT AGC AAC GTA 3′	470–447	

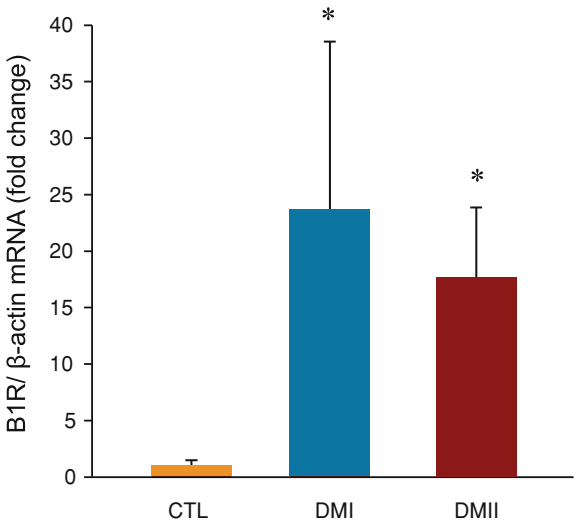


Fig. 5.4 Expression of B1R in retinas of control, type I, and type II diabetic human donors. The expression of B1R mRNA was increased in the retina of type 1 and type 2 diabetic donors but not detectable in the retina of control. Data are expressed as mean ± SEM of B1R mRNA as a ratio with the reference gene β-actin. Retinae were obtained from four controls, four patients with type 1 diabetes and five patients with type 2 diabetes. Medical status of patients is given in Table 5.2. *CTL* control, *DMI* type I diabetes mellitus, and *DMII* type II diabetes mellitus. Statistical comparison with control group is indicated by $P^* < 0.05$

5.4 Preventing or Reversing Retinal Damage in Diabetes by Drugs Targeting the Kallikrein-Kinin System

As the KKS is present in the vitreous and retina from people with NPDR and PDR, the findings suggest that the pro-inflammatory effects of BK and its receptors may contribute to the development of sight threatening features of diabetic retinopathy such as the DME, blood flow deregulation, and neovascularization. Pharmacological strategies have been developed to either inhibit the kallikreins or antagonize the kinin receptors (Table 5.3).

Table 5.2 Medical history of diabetic and control donors of retina

	Gender	Age	Cause of death	Medical history	PE time (h)
Control donors					
1	M	70	Lung cancer	Prostate cancer, COPD, HTN, HLD	6.1
2	M	65	Pancreatic cancer	Pleural effusion	6.3
3	M	64	Lung cancer	COPD, osteoporosis, ETOH abuse	8.3
4	M	64	Encephalopathy	Esophageal cancer métastasés to brain	10.7
Diabetes type I					
1	F	71	Liver failure	HTN, hypokaliema, ETOH abuse	9.8
2	M	58	Cardiovascular disease	HTN, HL, A-FIB, smoker	9.8
3	M	70	CVA	HTN, epilepsy	6.2
4	M	52	Coronary artery disease	Diabetes type I	7.2
Diabetes type II					
1	M	69	Pneumonia	HTN, HL, A-FIB, COPD	11.5
2	F	70	Ventricular tachycardia	HTN, coronary artery disease, DR	9.2
3	M	66	Gastrointestinal bleed	HTN, HL, CVA, prostate disease, bipolar	11.6
4	M	57	Lung cancer	COPD	7.3
5	F	56	Intracrania Hemorrhagel	HTN, HL, ESRD,CKD, anemia, acidosis	5.8

The retinas were obtained from the Eye Bank for Sight Restoration, New York, USA. The medical status of subjects is provided as follows: *COPD* chronic obstructive pulmonary disease, *HTN* hypertension, *HLD* hypersensitivity lung disease, *ETOH* alcoholic lung disease, *HL* Hodgkin's lymphoma, *A-FIB* atrial fibrillation and heart disease, *CVA* cerebrovascular accident, *ESRD* end-stage renal disease, and *CKD* chronic kidney disease. The post-enucleation (PE) time after death was between 6–12 h

5.4.1 Involvement of the Kallikrein-Kinin System in Vascular Permeability Changes and Macular Edema

There is strong evidence that the increased retinal plasma extravasation and BRB breakdown is blocked by selective kinin B1R and B2R antagonists in STZ diabetic rats (Lawson et al. 2005; Simard et al. 2002; Abdouh et al. 2008; Pouliot et al. 2012; Catanzaro et al. 2012). In addition, increased retinal vascular permeability induced by intravitreal injection of BK is inhibited by the B2R antagonist Hoe-140 (Abdouh et al. 2008). Catanzaro et al. (2012) also reported the association of increased NO levels and B1R related to vascular hyperpermeability in the retina of 12-week-old STZ-induced diabetic mice. Using non-systemic and non-intravitreal methods, we showed that ophthalmic drops application of a non-peptide B1R antagonist, LF-22-0542, could prevent vascular hyperpermeability (Pouliot et al. 2012) and compelling evidence suggests that iNOS is likely involved in this pathway (Fig. 5.3).

Table 5.3 Synopsis of the current antagonists for kinin receptors

B1R antagonist	
Lys-Leu8-des-Arg9-BK	Regoli and Barab (1980), Regoli et al. (1998)
Leu8-des-Arg9-BK	
R-715	Regoli et al. (1998)
Ac-Lys-[βD -Nal7, Ile8]des-Arg9-BK	
B9858	Mason et al. (2002), Stewart et al. (1997)
Lys-Lys-[Hyp3, Igl5,D -Igl7, Oic8]des-Arg9-BK	
SSR240612	Lacoste et al. (2013), Gougat et al. (2004)
Benzo-sulfonylamide compound	
LF22-0542	Pouliot et al. (2012), Porreca et al. (2006)
R-954	Gobeil et al. (2013)
Ac-Orn-[Oic2, α-MePhe5,D -βNal7, Ile8]des-Arg9-BK	
B2R antagonist	
HOE 140 (Icatibant)	Wirth et al. (1991), Sigurdsson et al. (2013)
D-Arg-[Hyp3, Thi5, D-Tic7, Oic8]Bk	Ferreira et al. (2013)
FR-173657	Pietrovski et al. (2011), Abe et al. (1998)
WIN64338	Meini et al. (2010), Sawutz et al. (1994)
LF 16-0687 (anatibant)	Simmon (2009), Pruneau et al. (1999)
CP0127 / Bradycor	Whalley et al. (2012)
D-Arg-Arg-Pro-Hyp-Gly-Phe-Cys-DPhe-Lue-Lue-Arg	
B1R/B2R antagonist	
B9430	Wang et al. (2010), Stewart (2004)
D-Arg-[Hyp3, Igl 5,D -Igl7, Oic 8]-BK	
B9870/ CU201/ Breceptin	Shaposhnikov et al. (2013), Stewart (2004)
D-Arg-Arg-Pro-Hyp-Gly-IgI-Ser-DIgI-Oic-Arg	

Inhibition of eNOS with *N*(G)-nitro-L-arginine methyl ester results in retardation of retinal vascular hyperpermeability and endothelium-dependent vasorelaxation (Bucci et al. 2005). Based on these findings, Phipps and Feener (2008) suggested a pathway (PK→BK→B2R→eNOS), which would contribute to vascular permeability and edema. The deficiency of C1-INH, the major inhibitor of FXII, in C1-INH null mice results in increased PK and FXIIa activities that increases BK production and B2R-mediated vasogenic edema (Han et al. 2002). Intravitreal injection of PK also increases retinal vascular permeability. A treatment with a selective PK inhibitor, ASP-440, blunts vascular permeability in rats with hypertension or STZ-induced diabetes (Clermont et al. 2011). As PK is strongly increased in the blood of diabetic patients, ocular hemorrhages occurring during diabetes might increase the pathological effects of PK. Injection of isolated components of blood (CA-1 and PK) into the vitreous could increase retinal vascular hyperpermeability and retina thickening (Gao et al. 2007; Clermont et al. 2011). Similarly, injection of autologous blood into the vitreous induces retinal

hyperpermeability and leukostasis, which are reduced by a PK inhibitor and mimicked by the injection of PPK/FXII/HMWK (Liu and Feener 2013). PK can also function as a plasminogen activator, which could contribute to plasmin-mediated fibrinolysis and activation of matrix metallo-proteinases (MMPs) (Selvarajan et al. 2001; Lund et al. 2006). Because PK is involved in thrombosis and blood hemostasis, it would be, however, highly risky to block PK systemically to treat DR.

At this time, it would be premature to exclude the contribution of TK that is expressed in diabetic retina and also because kinins are autacoids, which normally exert autocrine and paracrine functions.

5.4.2 *Involvement of the Kallikrein-Kinin System in Blood Flow Changes*

Kinins have been shown to cause vasodilatation, regulation of blood flow, stimulation of endothelial cell proliferation, and inflammatory responses (Marceau et al. 1998; Couture et al. 2001). In inflammatory conditions, kinins increase blood flow through the release of endothelial mediators such as NO and prostacyclin (Fig. 5.3b). However, there is no clear relationship between kinin and changes in blood flow during DR. Blood flow is also dependent on matrix metallo-proteinase (MMP) activity, consistent with BK action to promote acute release of constitutively expressed MMP-9 (Webb et al. 2006; Webb 2011). This raises the possibility that KKS may have a physiological role in the regulation of ocular blood flow in response to intraocular pressure changes, but also in ischemic preconditioning and in protection of ocular tissues against ischemic injury that is known to occur in DR.

Intravitreous injection of the selective and stable B1R agonist Sar-D-Phe^{8}des-Arg^{9}-BK increased significantly retinal blood flow as compared to baseline value when assessed by laser Doppler in diabetic rats (Hetu 2011). B1R displays a direct action on blood vessel endothelium as shown with selective B1R agonists, which caused dose-dependent vasodilation of retinal vessels in isolated retina of STZ diabetic rats (Abdouh et al. 2003). The response involved intracellular calcium mobilization and release of nitric oxide and prostaglandins in endothelial cells (Abdouh et al. 2003). A pharmacological in vivo study using a B1R antagonist highlighted the possibility that endogenous kinins can exert a protective vasodilation to maintain normal retinal blood flow at the very early stage of diabetes (Pouliot et al. 2011). This possibility is supported by the presence of kinin receptors in the inner and outer nuclear layers and ganglion cell layer of the retina (Ma et al. 1996; Pouliot et al. 2011).

5.4.3 Involvement of the Kallikrein-Kinin System in Neovascularization

The KKS enhances the concentration and signaling of the mediators of endothelial cell proliferation and migration (NO, VEGF, and fibroblast growth factor 2 (FGF2)) and thereby stimulates angiogenesis. Furthermore, it is shown that BK via B2R enhances the homing of circulating endothelial progenitor cells, which is another important source for the formation of new vessels (Zuccollo et al. 1996). HMWK promotes angiogenesis through release of BK by kallikrein (Colman et al. 2003). Through NO synthesis, B1R increases the expression of FGF2, which is pro-angiogenic via its receptor FGFR1 (Parenti et al. 2001). Neovascularization via B1R may be induced by the expression of VEGF and VEGFR-2 (Ikeda et al. 2004; Li et al. 2008). Whereas the B2R transactivates VEGFR-2 by phosphorylation of its cytoplasmic domain (Thuringer et al. 2002), B2R may increase the expression of VEGF and VEGFR-2 via PI3 kinase/Akt/GSK3beta signaling pathway (Yao et al. 2008).

The local delivery of BK and B1R selective agonists can induce neovascularization in the rabbit cornea (Parenti et al. 2001) and in the chicken chorioallantoic membrane (Colman et al. 2003). The intravitreal injection of a TK inhibitor, kallistatin, reduces retinal neovascularization in STZ diabetic rats, effects mediated by the VEGF system (Gao et al. 2003). In addition, Ebrahimian et al. (2005) reported a role for B2R in ischemia-induced retinal angiogenic responses. Hence, the mechanism of action of kinins in the formation of new vessels appears to include both kinin B1R and B2R on endothelial and other cells.

5.4.4 Interaction Between Kallikrein-Kinin System and Renin–Angiotensin System in the Diabetic Retina

Another strategy to prevent or treat DR would be to target the interaction between the RAS and KKS. The pro-oxidative RAS pathway enhances the expression of B1R by converging to the activation of NAPDH oxidase and NF-κB (Fig. 5.5). Components of RAS are present in ocular tissues, and RAS-mediated hypertension is an aggravating factor for DR (Ayalasomayajula et al. 2004). Pharmacological blockade of RAS attenuates most pathological pathways in DR and is accompanied by a downregulation of VEGF and VEGFR-2 (Wilkinson-Berka 2006). Angiotensin II increases the leakage of retinal blood vessels (Aiello et al. 1994) and stimulates the formation of new retinal blood vessels via upregulation of VEGF and other growth factors (Wilkinson-Berka 2006).

Angiotensin II and angiotensinogen levels are elevated in the vitreous fluid of PDR patients as compared with NPDR (Gao et al. 2007; Funatsu et al. 2002). Also these patients show greater serum concentrations of ACE and renin with the severity of DR, suggesting the involvement of both the local intraocular and

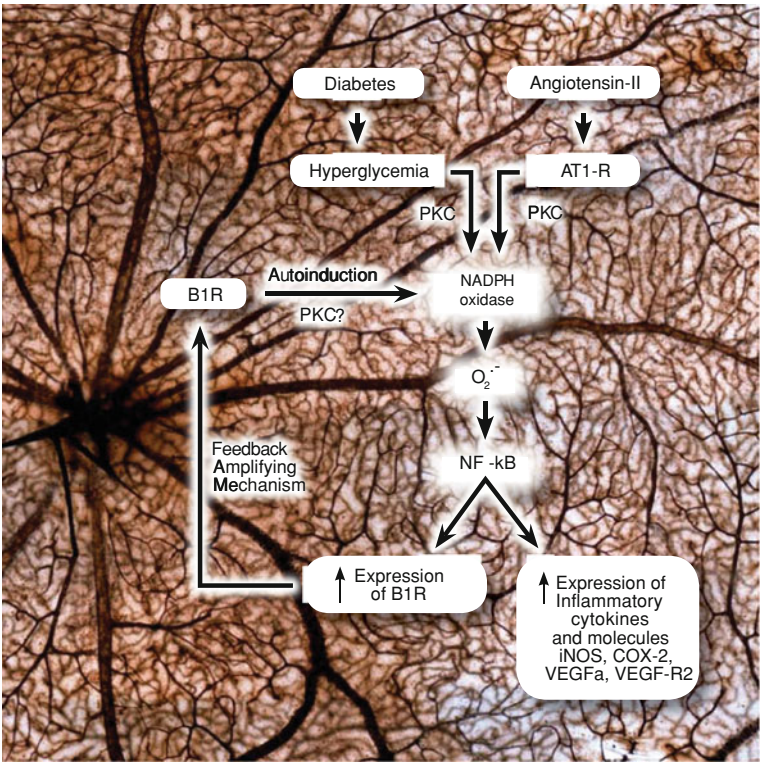


Fig. 5.5 Putative deleterious pathways associated with RAS in diabetic retinopathy. Both hyperglycemia and angiotensin II type 1 receptor (AT1-R) are known to activate NADPH oxidase via PKC to increase the production of ROS such as superoxide anion. This could enhance the expression of B1R and various inflammatory mediators, receptors, and enzymes (iNOS, COX-2, VEGFa, VEGF-R2, and cytokines) via the NF-κB pathway. Activation of B1R can intervene in a positive feedback loop to further increase the oxidative stress resulting in the upregulation of B1R (autoinduction) and overexpression of inflammatory molecules. Hence, B1R is expected to amplify and perpetuate the retinal inflammatory process. *B1R* bradykinin receptor 1, *VEGF* vascular endothelial growth factor, *VEGFα* vascular endothelial growth factor A, *VEGF-R2* vascular endothelial growth factor receptor 2, *PKC* protein kinase C, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase 2, $O_2^{\bullet-}$ superoxide anion, and *AT1-R* angiotensin II type I receptor

systemic RAS in DR (Clermont et al. 2006). AT1-R activation can stimulate several pathways involved in the pathogenesis of DR such as inflammation, oxidative stress, cell proliferation, pericytes migration, and remodeling of extracellular matrix by increasing matrix metallo-proteinases, angiogenesis, and fibrosis (Wilkinson-Berka 2006). The hypoxia-induced retinal angiogenesis is linked to the upregulation of RAS- and AT1-R-mediated induction of inflammatory mediators and growth factors, including VEGF and platelet-derived growth factor (Amano et al. 2003). Importantly, ACEI prevents the induction of vascular B1R expression

in a diabetic model (Ismael et al. 2008), suggesting that the beneficial effects of RAS blockers and ACEI in DR could be associated with B1R suppression (Fig. 5.5). This hypothesis is supported by studies reporting enhanced expression of kinin B1R in cardiovascular and neuronal tissues from rat models of angiotensin II-induced hypertension (Ceravolo et al. 2007; Fernandes et al. 2006; Kintsurashvili et al. 2001; De Brito Gariepy et al. 2013). This involves the activation of AT1-R that enhances the production of ROS causing the subsequent activation of phosphatidylinositol-3-kinase and NF-κB (Morand-Contant et al. 2010). Furthermore, AT1-R antagonism has been reported to exert beneficial vascular effects not only by reducing AT1-R signaling, but also by enhancing AT2-R signaling (Matsubara 1998; Regoli et al. 2012).

The AT1-R activation is also linked to the pathogenesis elements of DR such as leukostasis and neurodegeneration (Simo and Hernandez 2009). This is consistent with neuroprotection as a relevant mechanism involved in the beneficial effects of angiotensin receptor blockers in DR (Kurihara et al. 2008; Silva et al. 2009). Clinical studies have also demonstrated beneficial effect of RAS blockade on retinal permeability (Larsen et al. 1990; Chase et al. 1993). These findings could indicate a long-term beneficial effect on DR. Similarly, inhibiting ACE with perindopril, a common drug used for hypertension and diabetes treatment, attenuates VEGF-mediated BRB breakdown in STZ diabetic rats (Kim et al. 2009). On these experimental bases, it would be reasonable to postulate that RAS blockade can promote higher beneficial effects in DR than other antihypertensive agents.

5.5 Conclusion

Research in animal models has confirmed a key role for the KKS in pathophysiology of DR including vascular inflammation and hyperpermeability, oxidative stress, vascular alterations, and neovascularization. This is further supported by clinical studies showing overactivity of the KKS in the retina of diabetic patients. Thus far, pharmacological blockade of PK and kinin receptors has shown beneficial effects in rodent DR. Before moving to clinical settings, it is important to recall that B2R partakes to vasoprotection and PK to thrombogenesis and formation of kinins involved in vascular homeostasis. In contrast, no physiological function has been attributed to B1R and its occurrence is generally the signature of disease. Based on this reasoning, topical ocular application of B1R antagonists appears as a safer therapeutic approach for the treatment of DR. This is proposed as a more specific, noninvasive, and comfortable intervention that takes into account the biosynthesis of B1R ligands generated from both PK and TK pathways.

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Competing Interests The authors declare that they have no conflict of interest.

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