New trends and therapeutic approaches for the management of diabetic retinopathy

Diabetes mellitus is a growing epidemic that has become a global public health problem. The long-term complications of diabetes include retinopathy, the leading cause of blindness and visual impairment in adults. Diabetic retinopathy correlates with the duration of diabetes. Improved medical care of diabetic patients, and therefore increased life expectancy, will result in more instances of diabetes-induced blindness. Several innovative therapeutic approaches address the unmet need to prevent and treat this debilitating consequence of diabetes.

By Dr Didier Pruneau

Diabetes mellitus is a global and rising problem, with an estimated 220 million people worldwide currently affected. The diabetic epidemic will account for 300 million people suffering from diabetes in 2025, according to the World Health Organization. Diabetic retinopathy (DR) is a common microvascular complication of diabetes and a leading cause of blindness. After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment[1]. Forms of diabetic retinopathy include non-proliferative and proliferative diabetic retinopathy. Non-proliferative diabetic retinopathy (NPDR) is associated at early stages with retinal capillary occlusion, pericyte ghosts, capillary cell death, leukostasis, aneurysms, microvascular leakage, haemorrhage and to some extent neuronal cell death. This results in avascular hypoxic areas that trigger, through the release of hypoxia-inducible factor 1-a (HIF-1a) and vascular endothelial growth factor (VEGF), retinal neovascularisation, a hallmark of proliferative diabetic retinopathy (PDR). Thus, PDR consists in the proliferative growth and formation of new blood vessels that develop from the inner retinal circulation. These new vessels grow beyond the supporting structure of the retina and can even rupture and haemorrhage into the vitreous in response to a rise of the blood pressure. Consequently, this haemorrhage results in vision loss. The new blood vessels can also cause retinal detachments. Diabetic macular oedema (DME), manifested by the swelling of the retina due to the leakage of fluids from blood vessels into the macula (the highly pigmented spot near the centre of the retina), can occur at any stage of the disease. However, it is more frequently observed in PDR patients. Macular oedema does not cause total blindness but can lead to severe vision loss. PDR and DME account for 9% and 17% of all diagnosed diabetic retinopathy cases, respectively[2].

Current approaches to prevent and slow down the progression of diabetic retinopathy are built around the tight control of glucose and blood pressure, as demonstrated by the United Kingdom Prospective Diabetes study (UKPDS). Intensive metabolic diabetes therapy and blood pressure control lead to a reduction of the progression of diabetic retinopathy[3,4]. Still, patients with diabetes remain at high residual risk for microvascular complications, even if they are treated with optimal standard of care, a factor which certainly underscores the unmet need for novel therapeutic approaches to prevent and treat diabetes-induced blindness[5]. Today, therapies to treat diabetic retinopathy include laser-induced retinal photocoagulation, which still remains the first-line treatment of diabetic retinopathy. It reduces the risk of blindness derived from vitreous haemorrhage or detachment of the retina. This therapy has been shown to be successful for early treatment of proliferative diabetic retinopathy before the bleeding or detachment has progressed too far. Limitations of laser therapy include a diminished vision field and reduced colour vision and sensitivity. Vitrectomy, the surgical removal of the vitreous gel from the middle of the eye, is often used for patients with more advanced retinal disease. The procedure is intended to prevent the complete detachment of the retina (reviewed in [6]).

Existing treatment options for diabetic retinopathy are limited, resulting in a need for new therapeutic approaches to treat this debilitating disease. Current research is focused on understanding the molecular and biochemical mechanisms of the development and progression of diabetic retinopathy. Several pharmacological agents are currently studied for the treatment of diabetic retinopathy. These include local and systemic agents.

Diabetic retinopathy and angiogenesis

Angiogenesis plays a fundamental role in the normal development and pathological process of the eye. Hyperglycaemia, ischaemia and other growth factors can induce vascular endothelial growth factor (VEGF), a glycoprotein that is essential for the formation of the foetal vascular system. VEGF is expressed during embryonic development, and its expression decreases after birth, but it was also found to be highly expressed in rapidly growing tumours. VEGF is active in a wide variety of processes; it plays a prominent role in ocular neovascularisation and is active in promoting ocular inflammation. VEGF is increased by retinal hypoxia and induces the breakdown of the blood-retinal barrier, thus strategies to block VEGF or its activity in the eye may provide promising treatment options for diabetic retinopathy[6].

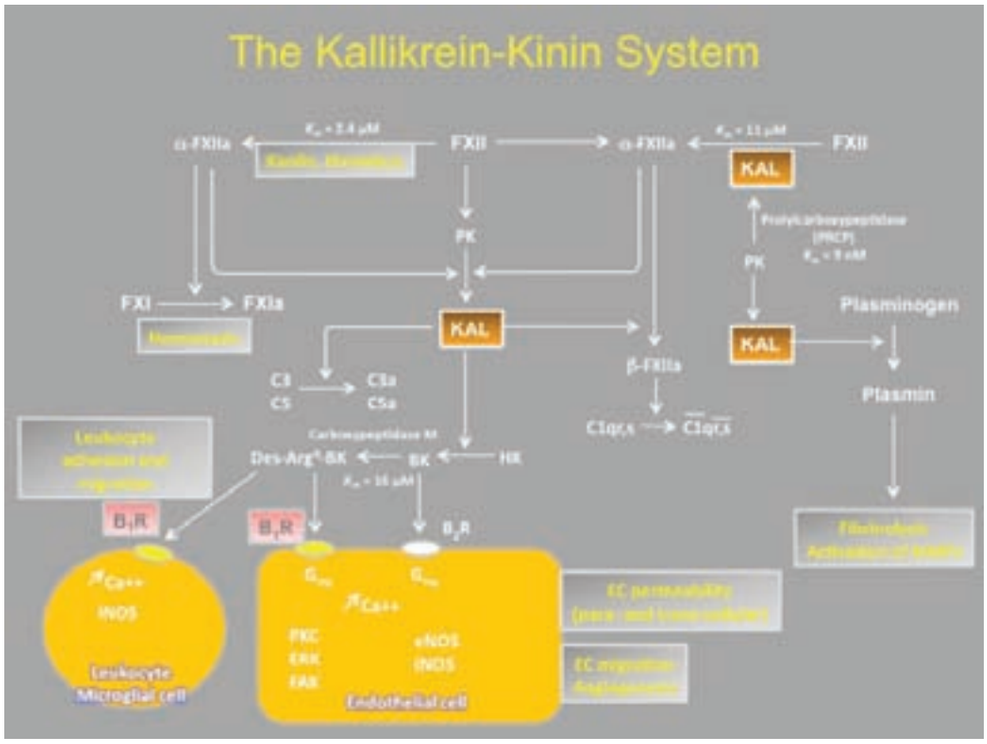

Figure 1: The kallikrein-kinin system

One of the first pharmacological approaches for treating diabetic retinopathy targets the vascular endothelial growth factor (VEGF). Anti-VEGF therapies are meanwhile important therapies for the management of several cancer types and other diseases that include wet age-related macular oedema (AMD). The latter is caused by the abnormal growth of blood vessels behind the retina under the macula. Currently, ranibizumab, pegaptanib, bevacizumab and VEGF Trap-Eye are in clinical trials to investigate local (ocular) agents for the management of diabetic retinopathy[7].

Ranibizumab is a recombinant humanised monoclonal antibody fragment that is directed against all isoforms of human VEGF-A. The US Food and Drug Administration (FDA) approved ranibizumab for wet AMD in June 2006, and studies are under way to investigate ranibizumab in DME.

Pegaptanib is a PEGylated (conjugated to polyethylene glycol) neutralising RNA aptamer that specifically targets the VEGF-A165 isoform. Intravitreal Pegaptinib showed some efficacy in DME, and the subset analysis of the Phase II clinical trial also demonstrated a regression of retinal neovascularisation in patients with PDR. Pegaptanib was approved by the FDA for the treatment of exudative AMD in December 2004.

Bevacizumab, approved by the FDA in February 2004 for the treatment of metastatic colorectal cancer, has been used as intravitreal bevacizumab for DME and PDR. Randomised clinical trials have shown that bevacizumab demonstrated favourable short-term anatomic and visual outcomes in patients with DME and short-term efficacy as an adjunct to photocoagulation in patients with PDR. It is noteworthy that some patients with PDR suffered from tractional retinal detachment after intravitreal treatment with bevacizumab[8].

VEGF-Trap-Eye is a recombinant fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PlGF). VEGF-Trap-Eye is currently in a Phase II study of a patient population with DME.

Hyperglycaemia is known to increase the formation of diacylglycerol and subsequently activates protein Kinase C (PKC), an upregulator of VEGF. First studies of ruboxistaurin, an orally administered inhibitor targeting protein kinase C (PKC)-β, showed that the drug was associated with a reduction of the progression of DME and a reduction of vision loss in patients with DME. The occurrence of visual improvement in patients with non-proliferative retinopathy also increased[9].

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Diabetic retinopathy and inflammation

Immunological processes play an important part in diabetic retinopathy. Diabetic retinopathy is characterised by typical features of low-level inflammation such as elevated levels of circulating and vitreous cytokines, chemokines and growth factors. Chronic retinal leukostasis, the increased adherence of leukocytes to the capillary endothelium, leads to vascular leakage and haemorrhage[6].

Thus, targeting inflammation is another investigational approach to target diabetic retinopathy. Corticosteroids, established anti-inflammatory agents, are able to slow the progression of diabetic retinopathy, as demonstrated by a recent study; however, the authors concluded that any treatment used routinely to prevent PDR should have a favourable safety profile considering the high incidence of elevation of intra-ocular pressure and cataracts associated with intravitreal steroids[10].

Corticosteroids are injected intravitreally, and various extended-release corticosteroids for the long-term treatment of DME are currently under investigation (ie Iluvien® and Ozurdex®).

The kallikrein-kinin system in diabetic retinopathy

The kallikrein-kinin system (KKS) is a multi-protein system that controls blood circulation and kidney function, and promotes inflammation and pain in pathological conditions. Plasma kallikrein triggers the contact cascade with its major components kallikrein and bradykinin. Kallikrein and the Hagemann factor (factor XIIa) autoactivate each other and subsequently stimulate the conversion of prekallikrein to kallikrein, leading the cleavage of high-molecular-weight kininogen (HMWK) to bradykinin. The biological downstream effects of the KKS are mediated by bradykinin, a peptide hormone that activates the G-protein coupled receptors (GPCRs), kinin B_1 and B_2 receptors (B_1R and B_2R). The B_2R is constitutively expressed in vascular and neuronal cells. The inducible B_1R plays a major role in neutrophil recruitment and chemotaxis[11-13] (**Figure 1**).

The activation of the kallikrein-kinin system has been shown to induce a host of proinflammatory responses.

Retinal inflammation is involved in the development of diabetic retinopathy, and accumulating evidence demonstrates a pivotal role for the KKS in the development of diabetic retinopathy. The KKS system is expressed in the human eye[14], and high levels of carbonic anhydrase (CA-1), prekallikrein, IL-1β, IL-8, TNFα and IL-6 were found in the vitreous of diabetic patients when compared to healthy volunteers. CA-1 induces retinal oedema and haemorrhage through activation of the KKS, and IL-1β, IL-8 and glucose upregulate the expression of B_1R in vessels and leukocytes[15].

Furthermore, B_1R messengerRNA (mRNA) was markedly increased in the retina of rats with streptozotocin (STZ)-induced diabetes[16]. Phipps et al were able to show that intravitreous injection of recombinant plasma kallikrein induced retinal oedema and haemorrhage in diabetic rats, whereas systemic treatment with a kallikrein inhibitor reduced retinal vascular leakage[17].

Recent studies have shown that FOV-2304, a non-peptide kinin B_1R antagonist, abolished retinal vascular permeability, as well as leukostasis and leukocyte infiltration, hallmarks of diabetic retinopathy, in streptozotocin-induced diabetic rats[18]. Additionally, diabetes-induced up-regulation of the many mRNAs, such as endothelial nitric oxide synthase (eNOS), nitric oxide (NO), B_1R, B_2R, VEGFα and VEGF receptor type 2, was reversed after seven days eye-drop treatment of FOV-2304[18]. Current studies are evaluating the convenient and safe eye-drop formulation of FOV-2304 in rabbits, a species with an eye volume similar to the human eye. The pharmacological blockade of the KKS system, in particular the kinin B_1R, may provide an innovative and promising treatment approach for diabetic retinopathy[19]. DDW

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